THE CANADIAN MEDICAL ASSOCIATION

LE JOURNAL DE

L'ASSOCIATION MÉDICALE CANADIENNE

JULY 29, 1961 • VOL. 85, NO. 5

IDIOPATHIC MEDIASTINAL AND RETROPERITONEAL FIBROSIS*

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IDIOPATHIC mediastinal fibrosis has been reported with increasing frequency in recent years. Here obstruction to superior mediastinal venous drainage is a striking clinical feature. The obstruction is due to a fibrous mass that engulfs and destroys some or all of the great veins uniting to form the superior vena cava. The disorder is rare but cases of superior vena caval obstruction by unexplained fibrous tissue have been reported at intervals for more than a century. John Hunter may have described the first case in 1757.[1]

In 1948 a retroperitoneal counterpart of this strange disorder was described.[2] The hallmark of idiopathic retroperitoneal fibrosis is an unusual dense retroperitoneal fibrotic lesion which envelopes and eventually constricts some or all of the structures in this region. Compression of the ureters is a prominent feature. To date 65 cases have appeared in the literature, most of them in urological publications.[3]

It is our purpose to discuss, briefly, the clinical and pathologic features of the two disorders and illustrate them with reports of three cases of our own. One of these had idiopathic mediastinal fibrosis, another idiopathic retroperitoneal fibrosis and the third showed clinical features and well-developed pathologic lesions of both conditions. Our findings lend support to the view that these two conditions are variants of a single disease process.

THE CLINICAL PICTURE

Idiopathic Mediastinal Fibrosis

The disease affects people of all age groups and both sexes, but has its greatest incidence in middle or later life. The onset is usually abrupt in individuals who have been healthy previously. Typically, the first symptom is slight swelling of the face and arms when the patient gets up in the morning. This often disappears in a few days only to recur at intervals of weeks or a few months. Superior vena caval obstruction becomes established within a year and there are added a dusky colour of the face and upper extremities, suffusion of the conjunctivae, dyspnea, giddiness, a feeling of pressure in the head and sometimes epistaxis or hemoptysis. These symptoms are aggravated by stooping, coughing, straining or exercise. The condition seems to be self-limiting but does not regress completely. As the years pass there is some clinical improvement due largely to the development of collateral circulation. The patient usually remains at work but is never completely free from symptoms. Fulminating, severe and even fatal cases have been described, and in these instances complicating thrombosis of the vena cava is thought to play an important role.

There is no pain or fever unless thrombosis complicates the picture. Pitting edema is present in the face, neck, arms and upper chest, but the rest of the trunk and lower limbs are normal. Distension of the superficial branches of the superior vena cava is the other prominent clinical feature. Pleural effusions sometimes occur and edema of the glottis is a rare complication.

The blood chemistry, blood counts, urinalysis and serological tests are all normal, as are the findings on bronchoscopic and esophagoscopic examinations. Radiographs of the chest reveal neither tumour nor infiltration in the lung fields. The mediastinum may be broadened by distension of the azygos and hemiazygos veins. The site of the venous obstruction can be demonstrated by mediastinal venography, but precise diagnosis rests ultimately on thoracotomy, biopsy of the fibrous tissue and exclusion of other causes of superior vena caval obstruction.

Idiopathic Retroperitoneal Fibrosis

Men are more commonly afflicted than women. The disease seems to have its greatest incidence in middle life but other age groups are susceptible also. As a rule the onset is insidious over a period of several months in previously healthy individuals.

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Presented at the 30th Annual Meeting of the Royal College of Physicians and Surgeons of Canada, Ottawa, January 20, 1961.

A few patients give a history of trauma to the abdomen or back, previous abdominal surgery or intra-abdominal inflammation. A dull aching pain in the flank, abdomen or back is the usual presenting symptom. It may be unilateral or bilateral and often radiates to the inguinal region or testes. Swelling of one or both legs and the scrotum, impotence, painless hematuria and anuria are other less frequent symptoms. In most instances there are added symptoms due to complicating infection of the urinary tract and renal failure. Moderate weight loss is usual as well.

Physical examination reveals few abnormal findings and these are not specific. Fever is rare and when present can be accounted for by complicating infection. The blood pressure is variable but is normal in most patients. Tenderness in the costovertebral angles or abdomen is present in about half the cases and occasionally an abdominal mass is palpable. Edema of the legs and scrotum, engorgement of the superficial veins of the abdomen and reduction in femoral pulses are sometimes encountered.

The results of laboratory investigations are likewise not specific. In the early stages, urinalysis, blood counts and blood chemistry may be normal. In many cases evidence of urinary tract infection or uremia will be present, and moderate anemia is often associated. Intravenous or retrograde pyelography usually reveals medial displacement of the ureters with hydronephrosis or a non-functioning kidney. The abnormalities may be unilateral or bilateral. Precise diagnosis rests on surgical exploration, biopsy of the fibrous tissue and exclusion of other causes of the obstructive uropathy.

This process too seems to be self-limiting and, when it ceases before extensive ureteral obstruction has led to irreversible renal failure, the patient may survive. Likewise, surgical relief of the ureteral obstruction may be live-saving.

PATHOLOGY

The pathology of the two conditions is strikingly similar and extraordinarily simple. In idiopathic mediastinal fibrosis there is a lump or plaque of hard, fixed, white fibrous tissue in the anterior mediastinum. The adjacent pleura is thickened but never invaded, nor are the pericardium, aorta, its branches, the trachea, esophagus and nerves, although they may be adherent to the mass and to one another. Only the great veins are involved. In idiopathic retroperitoneal fibrosis the dense plaque of fibrous tissue lies immediately anterior to the bodies of the lumbar vertebrae and the fascia covering the iliopsoas muscles. It may cross the midline and usually envelopes and progressively constricts some or all of the ureters, aorta, inferior vena cava and common iliac vessels.

Histologically the plaques of both conditions consist of dense collagenous fibrous tissue with some foci of chronic inflammatory cells. It has the general structure of a scar.

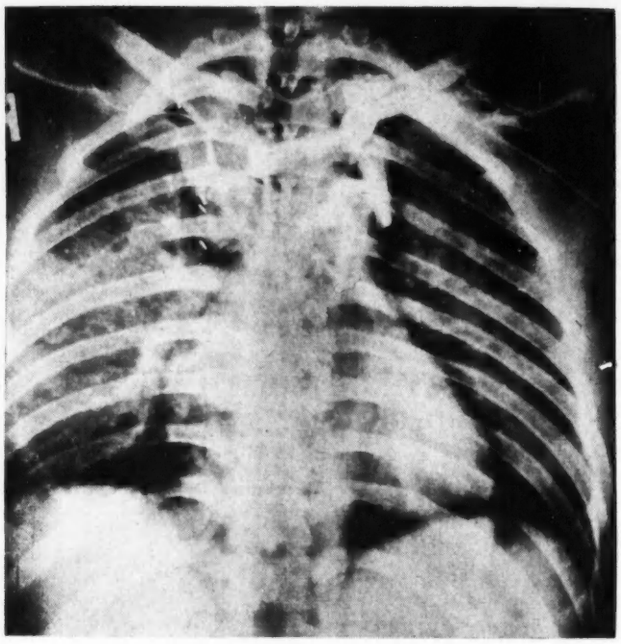

Fig. 1—(Case 1.) Superior vena cava venogram revealing obstruction of the vein and its tributaries.

CASE REPORTS

CASE 1.—*Idiopathic Mediastinal Fibrosis*

Early in 1957, a 20-year-old white man complained of swelling of his face and a sensation that blood was rushing to his head. These symptoms waxed and waned and were precipitated or aggravated by exertion, stooping and strong emotion. Fourteen years previously he had suffered a head injury in a fall which rendered him unconscious for an hour but following which he had no residual disability. There was no past history of other injury or serious illness.

Within a year the symptoms became more pronounced. There were added shortness of breath on exertion, swelling of the arms, a dusky colour of the face and the appearance of dilated veins over the upper arms, trunk and neck. In 1959 investigation at another hospital revealed similar clinical findings—the typical picture of superior vena caval obstruction. The blood counts, blood chemistry and urinalysis were all normal. Radiographs of the chest showed some widening of the upper mediastinum. Tomograms of the upper mediastinum, barium examination of the esophagus, bronchoscopy and bronchograms failed to clarify the diagnosis. Biopsies of the cervical and scalene nodes revealed non-specific lymphadenitis. At thoracotomy the surgeon encountered a hard, fixed, white plaque of tissue which had engulfed the great veins and surrounded the esophagus. Concluding that this was an inoperable sarcoma, he took a biopsy but did not attempt to resect the whole mass. Histologic examination revealed nothing but inflammatory granulation and scar tissue.

The patient was admitted to the Queen Mary Veterans Hospital, Montreal, in September 1960. There had been some alleviation of symptoms but he still showed the clinical picture of superior vena caval obstruction. Additional studies showed elevation of venous pressure in the arms (32 cm.) and prolongation of the arm to tongue circulation time (23 sec.). Venography of the superior vena caval system revealed

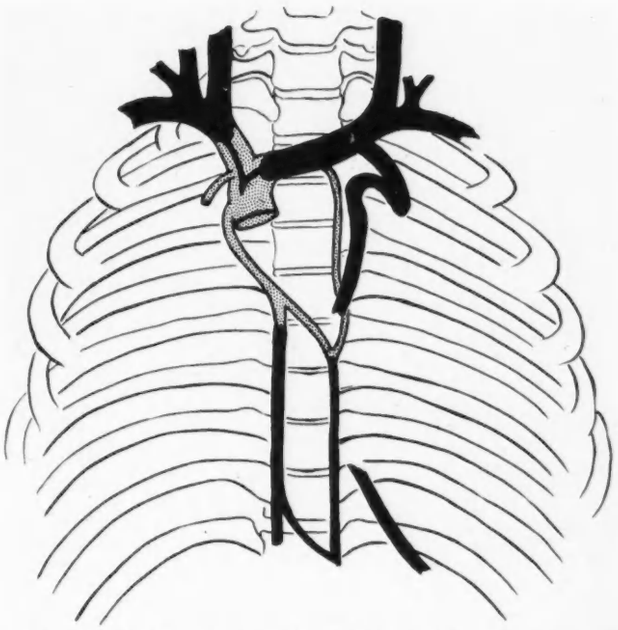

Fig. 2.—(Case 1.) Schematic representation of venogram shown in Fig. 1.

obstruction of the vein and its tributaries (Figs. 1 and 2).

He is still at work although he continues to suffer some disability from the venous obstruction.

CASE 2.—*Idiopathic Retroperitoneal Fibrosis*

A 49-year-old white man had complained of severe back pain, bilateral flank pain and a 20-lb. weight loss over a period of several months when he was admitted to the Queen Mary Veterans Hospital in 1949. His past health record had been excellent, marred only by an attack of typhoid fever in 1919 and a back injury in 1942 which kept him in bed for a few days. At the time of admission no local cause was found to account for his symptoms. Physical examination disclosed a firm, non-tender, immobile, midline abdominal mass. There were no other abnormal findings. Urinalysis, blood counts and blood chemistry were all normal, as was an intravenous pyelogram. At laparotomy a hard, pale mass was found in the retroperitoneal space extending from the brim of the pelvis to the crura of the diaphragm and surrounding both iliac arteries. In view of the proximity to the great vessels, no biopsy was taken. A lymph node removed from the greater omentum showed non-specific lymphadenitis. The patient was thought to have lymphosarcoma, and irradiation therapy totalling 6000 r was directed to the abdominal and lumbar regions. The abdominal mass was not altered but there was some improvement in his general condition. The pain subsided, he gained weight and remained in reasonable health for 10 years. In 1959 he was assailed by fatigue, began to lose weight and noticed that his ankles and feet were swelling. Early in 1960 he reported to the hospital and was re-admitted. On examination he seemed pale and chronically ill. His temperature was 98° F., pulse rate 96 per minute and blood pressure 130/75 (arms) and 170/100 (legs). There was pitting edema of both legs to the knees. Conspicuous dilated veins drained from the inguinal regions to the lateral thoracic wall. The right kidney was palpably enlarged and the hard abdominal mass was still present. The jugular veins were not distended. Urinalysis showed marked proteinuria with many leukocytes present. There was a moderate anemia (Hb. 8.5 g. %) and leukocytosis (13,000 per c.mm.); the sedimentation rate (22 mm. per hour) was elevated. Plasma proteins were normal. A clinical diagnosis of idiopathic retroperitoneal fibrosis was made.

Retrograde pyelography showed dilatation and medial displacement of the right ureter and marked hydronephrosis of the right kidney. A catheter could not be passed up the left ureter, but dye injected into the lower third showed that it too was displaced medially (Fig. 3). Exploration of the left kidney was

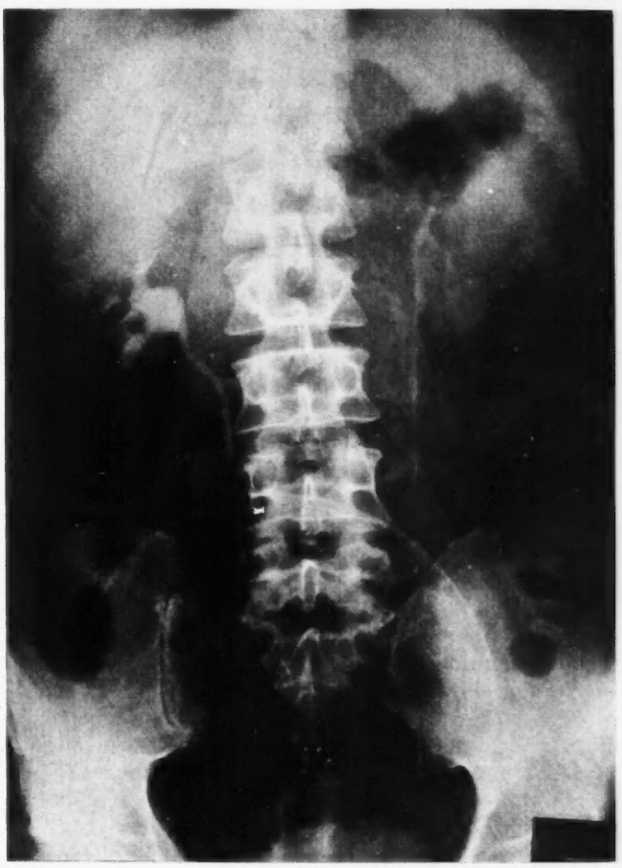

Fig. 3.—(Case 2.) Pyelogram demonstrating hydronephrosis of right kidney and medial displacement of the corresponding ureter.

followed four weeks later by exploration of the right kidney. The operations revealed dense fibrous tissue which had encased the lower poles of the kidneys and constricted the ureters. Biopsies of the periureteric tissue showed it to be dense, poorly vascularized fibrous tissue. Attempts to free the ureters were not successful and nephrostomies were fashioned. These drained well and the blood urea nitrogen dropped but never returned to normal levels. The subsequent course was complicated by deep femoral vein thrombosis on the right side and recurrent bouts of urinary tract infection despite the continuous use of urinary antiseptics and antibiotics. In the 11 months since the last operation he has been re-admitted on three occasions to change the nephrostomy tubes. He is up and about at home and attends the clinic regularly, but he remains chronically ill and is unable to work.

CASE 3.—*Idiopathic Mediastinal and Retroperitoneal Fibrosis*

A 29-year-old white man complained of swelling of his legs in 1956. At another hospital he was found to have chronic cystitis, a left pleural effusion, edema of both legs and arterial insufficiency of the right lower limbs. Arterial spasm was suspected and a right lumbar sympathectomy was performed via the anterolateral extraperitoneal approach. At operation there was edema of the skin and subcutaneous and retroperitoneal tissues. There was thrombophlebitis of the vena cava which was adherent to neighbouring structures and occluded by an organizing thrombus. The vein was ligated and a biopsy was taken from it. Histologic examination of the vein confirmed the surgical finding. After the operation, edema of the legs subsided but never cleared completely. The arterial insufficiency was relieved and the pleural effusion disappeared. He never felt completely well but his general condition was reasonably good and he was able to resume his work on the assembly line of a factory. During the year that followed he noticed intermittent swelling of his hands. In December 1957 pain in the right testis and swelling of the scrotum and legs prompted his readmission. Examination at that time revealed edema of the hands, genitalia and legs, ascites and bilateral pleural effusions. A right hydrocelectomy was performed. No firm diagnosis was established but a collagen disease was suspected.

Again there was remission of symptoms. The pain subsided and the edema decreased but intermittent swelling of the hands and feet persisted. He remained at work for another year. Early in 1959 the edema began to increase. Within a month he developed swelling of the face and hands as well as gross swelling of the lower limbs and genitalia. On admission to the Montreal General Hospital at that time he was pale and slightly cyanosed and seemed poorly nourished. His temperature was 98° F., pulse rate 82 per minute and blood pressure 145/115 mm. Hg. The jugular veins were prominent and there were many dilated superficial veins over the shoulders, anterior and lateral parts of the trunk and abdomen draining cephalward. Slight swelling of the face and hands was noted, and edema of the lower extremities extended up to the umbilicus. The left testis was enlarged and hard. The abdomen was swollen with ascites. Arterial pulses in both lower extremities were present but weak. The urine contained protein, red cells, leukocytes and scattered hyaline and granular casts. The blood urea nitrogen (21 mg. %) and the creatinine (2.5 mg. %) were slightly elevated. There was moderate anemia (Hb. 10.3 g. %) and leukocytosis (12,000 per c.mm.). Urine cultures grew *Staph. pyogenes, Strep. fecalis* and *Strep. pyogenes.* Radiographs of the chest revealed bilateral pleural effusions and prominent hilar shadows. A barium series was normal. Intravenous pyelography showed a marked right hydronephrosis and a non-functioning left kidney. Retrograde pyelography revealed bilateral hydronephrosis. The ureters were displaced medially and dilated in their upper thirds (Fig. 4). Suspicion of malignancy in the left testis led to its removal. A normal testis was found encased in a thick indurated band of white fibrous tissue.

A critical review of the problem at this juncture led to a clinical diagnosis of idiopathic retroperitoneal and mediastinal fibrosis. Although unprecedented, there seemed no other single diagnosis which could account for such disparate findings as superior vena caval obstruction, inferior vena caval occlusion, arterial insufficiency in the lower limbs and bilateral ureteral obstruction. A laparotomy was performed to settle the matter, and the diagnosis was established at once. The ureters were incorporated in the characteristic wide band of thick fibrous tissue. It was not possible to free them through the anterior approach. Biopsies were taken and the abdomen was closed.

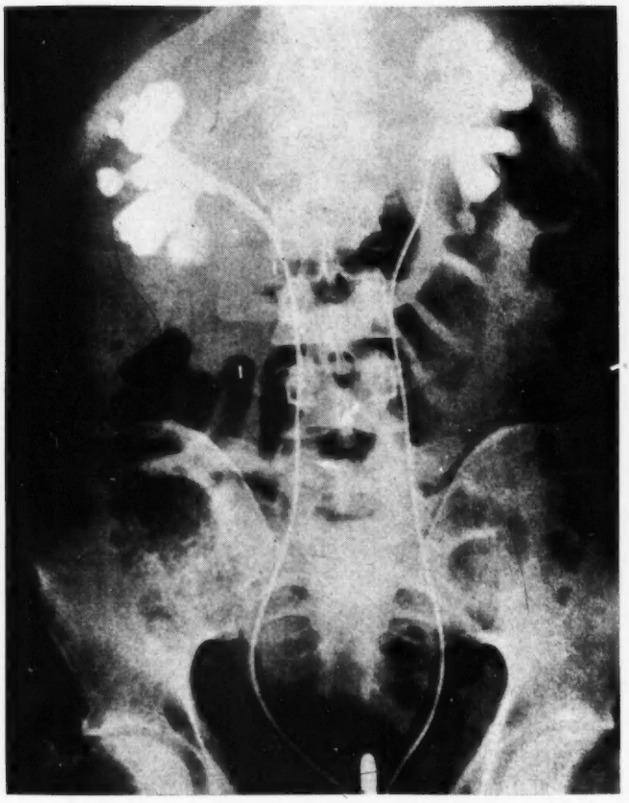

Fig. 4.—(Case 3.) Retrograde pyelogram showing bilateral hydronephrosis and medial displacement of ureters.

The patient survived for nine months. Following the laparotomy, cortisone was administered in doses of 100 mg. per day but had to be discontinued three weeks later because of increasing fluid retention. Shortly thereafter a pericardial friction rub became audible and the patient developed congestive cardiac failure which was controlled by digitalis and diuretics. Adequate urine flow was maintained, but the blood urea nitrogen level began to climb slowly. A left ureterocystotomy five months later failed to check the increasing nitrogen retention. A right ureterolysis and ureterostomy four weeks later was followed by a fall in the blood urea nitrogen from 70 mg. % to 50 mg. %. His clinical condition continued to deteriorate and the patient died quietly three weeks later.

Autopsy Findings

At autopsy numerous fibrous adhesions were encountered in the right side of the abdomen. Retroperitoneally, a thick indurated band of white tissue in front of the vertebral column extended from the floor of the true pelvis below, into the mediastinum above, and from one side of the trunk to the other. All the structures in the retroperitoneum were incorporated in this mass. The inferior vena cava was obliterated. The abdominal wall, aorta and common iliac

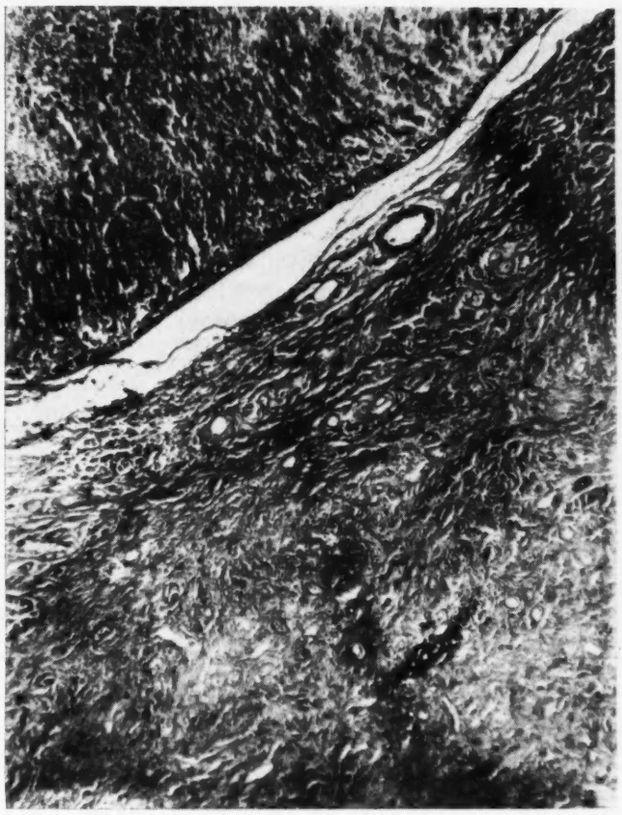

Fig. 5.—(Case 3.) Retroperitoneal fibrous mass fused with the adrenal gland capsule.

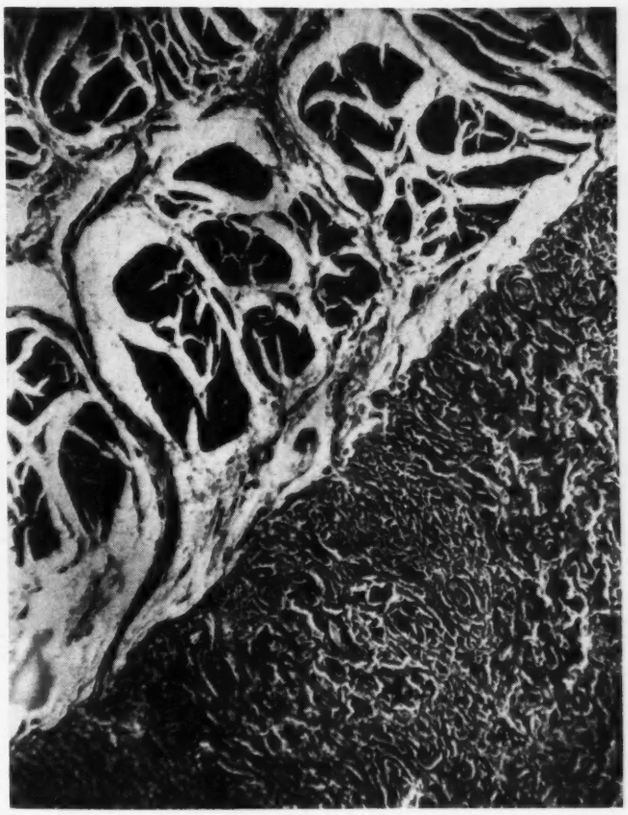

Fig. 7.—(Case 3.) The mediastinal fibrous mass merging with the muscular coat of the esophagus.

arteries were entirely surrounded, as were the ureters, pancreas and adrenals. There was bilateral hydronephrosis. The upper parts of the ureters were dilated as well and the renal cortices were thinned. Identical fibrous tissue encased the right testis and epididymis. On review of the specimen there was similar involve-

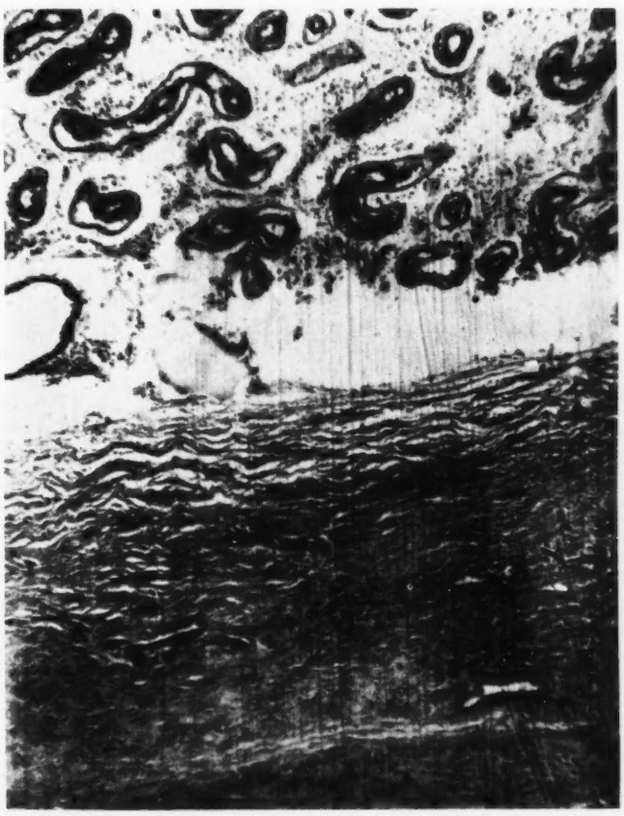

Fig. 6.—(Case 3.) Fibrous mass fused with the tunica albuginea of the testis.

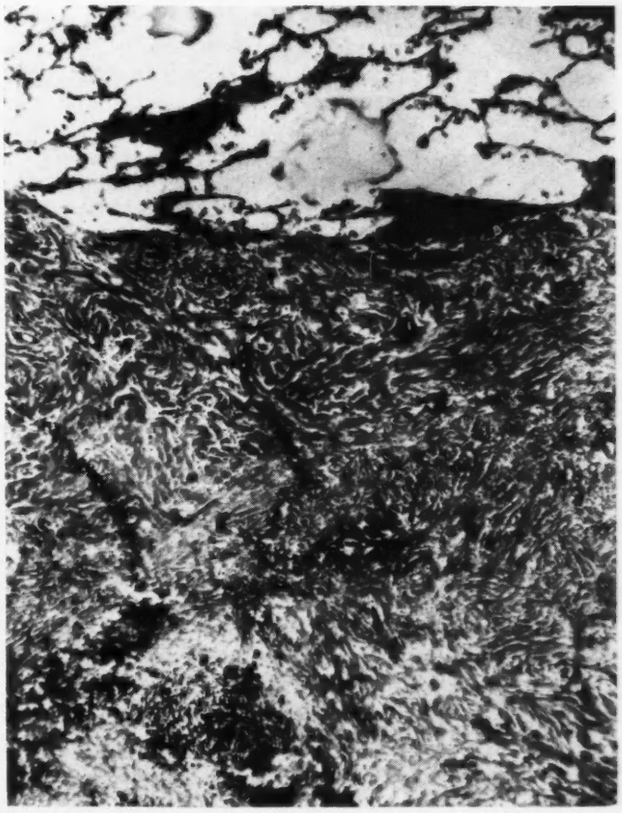

Fig. 8.—(Case 3.) The mediastinal fibrous tissue fused with the pleural membrane of lung.

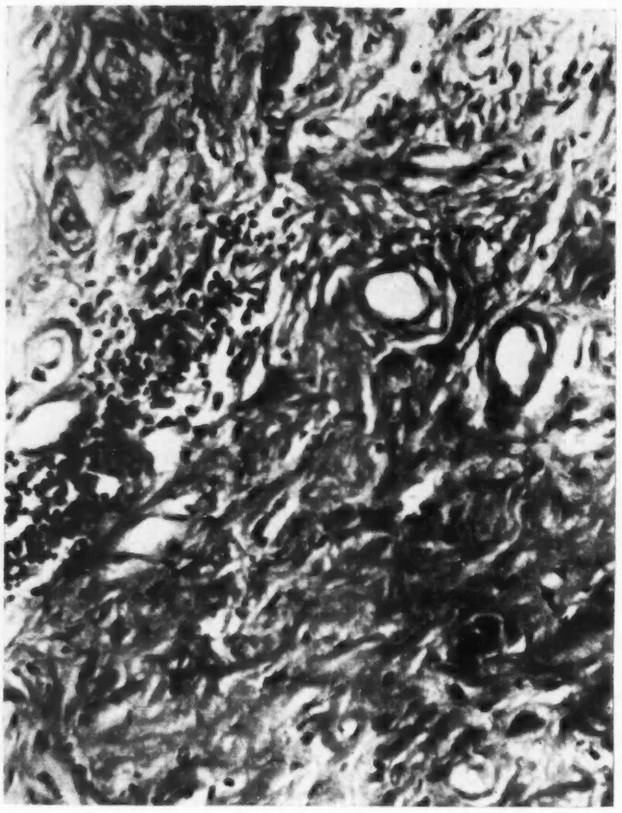

Fig. 9.—(Case 3.) The mature fibrocollagenous structure of the retroperitoneal fibrosis with scattered small blood vessels and occasional foci of chronic inflammatory cells.

ment of the left testis which had been removed surgically. The fibrous tissue surrounding the testes was limited to the scrotum. However, the main fibrous plaque extended in direct continuity from the pelvis to the superior mediastinum. In the thoracic cavity the fibrous plaque surrounded and compressed the superior vena cava. The aorta, pulmonary artery, trachea, main bronchi and esophagus were incorporated in the mass of fibrous tissue as well. The adjacent pleura was intimately bound to the parietes and diaphragm. The pleural spaces and pericardial sac were obliterated. The heart and lungs were normal.

Histologic examination revealed identical fibrous tissue in all sites (Figs. 5-9). Varying degrees of maturity and cellularity were apparent. There was some perivascular lymphocytic cuffing. Hemosiderin was not demonstrable. Sections of the kidneys showed evidence of chronic pyelonephritis.

DISCUSSION

Idiopathic mediastinal fibrosis and idiopathic retroperitoneal fibrosis, hitherto rare disorders, are being reported with increasing frequency. The pathologic lesion is strikingly similar if not identical in the two conditions and can be differentiated only by its site. The cause of each remains obscure despite suggestions that trauma, occult infection, organization of hematomata, and vascular disorders are responsible.[4, 5] Fatal outcomes have been recorded, but in general the two disorders seem to be self-limiting. This makes it difficult to assess the value of corticosteroid therapy, irradiation and the use of antibiotics, although success has been reported following the use of these agents. In idiopathic retroperitoneal fibrosis there is no doubt that early diagnosis and surgical release of strangled ureters can be life-saving.

Our third case is unique in demonstrating direct continuity of this strange fibrosis from the region of the pelvis to the superior mediastinum. We can find but one comparable example in the literature.[6] In this case, an autopsy revealed typical mediastinal and retroperitoneal plaques, but there was no direct continuity between them. Moreover, the clinical findings were related to the mediastinal lesion, and the retroperitoneal plaque was an unsuspected autopsy finding. In our case clear-cut clinical features of both disorders were present. Finally, the distribution of the lesion in our case lends strong support to the view that idiopathic mediastinal fibrosis and idiopathic retroperitoneal fibrosis are variants of a single disease process.[7, 8]

SUMMARY AND CONCLUSIONS

The disparate clinical findings and strikingly similar pathologic lesions of idiopathic mediastinal fibrosis and idiopathic retroperitoneal fibrosis have been reviewed briefly.

One further case of each condition has been reported.

An additional case has been reported showing clinical features and well-developed pathologic lesions of both disorders.

Our findings lend support to the view that the two conditions are variants of a single disease process.

The authors are indebted to Drs. G. W. Halpenny, A. D. MacDonald, J. T. MacLean and S. A. MacDonald.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

A consideration of the conditions which made for progress in scientific medicine has led me to speak for a little of conservatism in surgery. To say that one is a conservative surgeon is at once taken to be a guarantee of safety and security. It means that one does not readily abandon old and apparently well-established principles. Generally speaking, confidence in an individual of this type is well placed, and the more conservative a man is, the more likely is he to maintain the confidence of the public. Unfortunately, however, the indulgence of pure prejudice often passes as conservatism. It is surely wise that we should harbour no prejudices and that our cherished conservatism should in no way hinder our better judgement.—A. Primrose: 1911 Address in Surgery to the Canadian Medical Association, *Canad. M. A. J.*, 1: 591, 1911.

EARLY DIAGNOSIS OF ACUTE PULMONARY EMBOLISM*

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The desirability of a procedure for the early confirmation of suspected pulmonary embolism is emphasized by the reported 4% to 14% discrepancy between the final clinical diagnosis and necropsy findings.[1, 2] Diagnosis in the first 24 hours of illness is even less certain. Radiological examination[3-6] and electrocardiographic changes,[7-9] while helpful in some cases, are not usually sufficiently specific to provide the desired diagnostic confirmation. The three chief disturbances which commonly result from sudden occlusion of a large branch of the pulmonary artery are hyperventilation, oxygen unsaturation of the arterial blood and dissociation between the carbon dioxide tension of arterial blood and that of end-tidal air. This communication reports the results of a study designed to assess the value of the determination of the last-mentioned disturbance in the diagnosis of pulmonary embolism.

In 1957, Severinghaus and Strupfel[10] reported the reduction of end-tidal air carbon dioxide tension by air embolism. In 1959, Robin and co-workers[11] described a method for simultaneous determination of end-tidal air and arterial blood carbon dioxide tensions. A significant difference between these carbon dioxide tensions was noted in patients with acute pulmonary embolism. Because of the nature of the apparatus, the method used was not easily applicable to regular use in hospital wards. The work of Julian *et al.*[12] confirmed Robin's findings by demonstrating that unilateral pulmonary artery occlusion in dogs caused a significant reduction in end-tidal air carbon dioxide tension, whereas the arterial blood carbon dioxide tension remained within normal limits.

The carbon dioxide tension of end-tidal air and arterial blood in normal individuals is nearly the same. Acute pulmonary artery occlusion results in an area of lung which continues to be ventilated but is unperfused. Gas exchange across the alveolar-capillary membrane ceases, so that the alveolar pCO_2 tension in this area of the lung approximates that of the atmosphere. The carbon dioxide tension in end-tidal air will thus be lowered because of dilution caused by the gas derived from the affected area mixing with the gas contributed by the normal portions of the lungs.

Acute occlusion of a branch of a pulmonary artery also results in a mechanical redistribution of the right ventricular output to the unaffected area of the lungs. Thus the pulmonary capillary blood flow through the normal portions of the lungs is augmented. The effective alveolar ventilation must be increased if the arterial gas tensions are to be maintained at normal values.[13] In the absence of complicating factors, hyperventilation occurs and is generally of sufficient degree to maintain the arterial CO_2 tension at normal or even slightly lower than normal levels.

The experience in 60 patients in whom the end-tidal air and arterial carbon dioxide tensions were determined simultaneously is presented.

Material

The patients from the wards of the Victoria General Hospital, Halifax, were selected as follows:

1. Thirty-five patients who on admission or during the course of their stay in hospital developed sudden precordial distress and/or dyspnea. All were studied within 24 hours of the onset of these symptoms.

2. Twenty-four patients with a variety of diseases, but without acute distress, were selected at random.

3. One patient was studied during right heart catheterization.

Methods

As the result of the history and physical examination, a provisional diagnosis was recorded. A final diagnosis was later established on the basis of the course of the illness, critical diagnostic procedures other than pCO_2 values or necropsy examination.

The mean end-tidal pCO_2 was derived from duplicate determinations done at the patient's bedside using the Collins pCO_2 gas analyzer as described by Ravin and Stein.[14] Simultaneously, arterial blood was obtained from a brachial artery and its pCO_2 was determined immediately by the method of Astrup.[15] As the validity of such arterial carbon dioxide tension determinations depends upon the accuracy of the pH measurements, the pH meter was required to have an accuracy of $\pm$ 0.003. The maximum deviation of the arterial carbon dioxide tension should, therefore, not be in excess of $\pm$ 2% of its true value.

Prior to acceptance for clinical use, the Collins pCO_2 analyzers were compared with the Roughton-Scholander micrometer gas analyzer[16] at eight different carbon dioxide tensions ranging from 10 to 65 mm. Hg, and a mean difference between the two methods of less than 1.5 mm. Hg was the adopted standard. This necessitated frequent laboratory checks of the Collins analyzers. Thirteen such comparisons were made during the eight months of the study, with mean differences of 1.1 to 1.5 mm. Hg in ten of these. An example is given in Table I. On three occasions the mean difference exceeded 1.5 mm. Hg. In each instance the analyzer required factory repair, twice

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TABLE I.—pCO_2 of Gas Mixtures (mm. Hg)

Scholander	*Collins*
62.4	61.0
55.5	55.0
47.7	46.5
40.1	39.0
33.9	32.0
25.4	24.0
20.6	18.5
15.0	13.0
Mean 37.5	36.1
Mean difference.....	1.4

because of acid corrosion of the needle valve and once because of a leak at the point of insertion of the pressure gauge.

The inherent difficulty in assuring that samples of end-tidal air obtained for pCO_2 determinations are truly representative of alveolar air is well recognized.

Because of these factors, a pCO_2 difference of less than 5.0 mm. Hg between end-tidal air and arterial blood was not accepted as indicative of acute pulmonary embolism.

Results

Table II shows the results and final clinical diagnosis obtained in 24 patients without any acute distress. The arterial pCO_2 values ranged from 35.0 to 50.0 mm. Hg. The end-tidal air pCO_2 ranged from 34.0 to 46.0 mm. Hg. The difference between arterial and end-tidal pCO_2 values is slight in each instance despite the wide range of individual results. The greatest differences of 4.0 and 4.5 mm. Hg were obtained in two patients with emphysema and bronchiectasis.

TABLE II.—No Acute Distress

Pt. No.	*pH*	*$PaCO_2$ mm. Hg*	*$PACO_2$ mm. Hg*	*ΔPCO_2 mm. Hg*	*Diagnosis*
1	7.49	41.5	40.0	1.5	Rheumatic heart disease
2	7.43	46.0	44.0	2.0	Rheumatic heart disease
3	7.41	41.0	39.0	2.0	Rheumatic heart disease
4	7.43	37.0	36.0	1.0	Arteriosclerotic heart disease
5	7.46	40.0	39.0	1.0	Arteriosclerotic heart disease
6	7.44	39.0	38.0	1.0	Arteriosclerotic heart disease
7	7.40	42.0	41.0	1.0	Arteriosclerotic heart disease
8	7.43	40.0	38.5	1.5	Congenital pulmonary stenosis
9	7.43	39.0	37.0	2.0	Carcinoma of bronchus
10	7.44	46.5	42.0	4.5	Bronchiectasis
11	7.43	44.0	43.0	1.0	Bronchiectasis
12	7.46	40.0	39.5	0.5	Asthma
13	7.43	35.0	34.0	1.0	Bronchitis
14	7.37	40.0	37.0	3.0	Sarcoidosis
15	7.36	50.0	46.0	4.0	Emphysema
16	7.44	38.0	36.0	2.0	Carcinoma of bronchus
17	7.43	40.0	39.0	1.0	Pharyngitis
18	7.45	41.0	38.5	2.5	Hodgkin's disease
19	7.44	39.0	38.0	1.0	Carcinoma of stomach
20	7.45	41.5	40.0	1.5	Peptic ulcer
21	7.40	42.0	40.0	2.0	Diabetes
22	7.45	36.0	34.0	2.0	Common bile duct stricture
23	7.45	38.5	37.0	1.5	Menorrhagia
24	7.40	40.0	37.5	2.5	Peptic ulcer

Table III gives the results obtained in 19 patients who presented with a sudden onset of precordial distress and/or dyspnea. A provisional diagnosis of acute pulmonary embolism was recorded in seven of these patients, but a final diagnosis other than pulmonary embolism was subsequently established. Four patients had acute myocardial infarction; and three, Coxsackie B5 pleuritis. It is again evident that the end-tidal air/arterial pCO_2 difference in the individual patients studied is small.

TABLE III.—Acute Myocardial Infarction

Pt. No.	*pH*	*$PaCO_2$ mm. Hg*	*$PACO_2$ mm. Hg*	*ΔPCO_2 mm. Hg*	Diagnosis
25	7.49	38.5	35.0	3.5	Acute myocardial infarction
26	7.50	36.0	34.0	2.0	Acute myocardial infarction
27	7.47	38.0	36.0	2.0	Acute myocardial infarction
28	7.43	41.0	40.0	1.0	Acute myocardial infarction
29	7.41	40.5	39.0	1.5	Acute myocardial infarction
30	7.46	47.0	44.0	3.0	Acute myocardial infarction
			Acute Pulmonary Disease		
31	7.46	43.0	41.5	1.5	Pleuritis
32	7.43	46.0	43.0	3.0	Pneumonitis
33	7.44	37.5	37.0	0.5	Pneumothorax
34	7.38	30.0	28.0	2.0	Pleuritis
35	7.50	33.0	32.0	1.0	Pulmonary infarction
36	7.51	44.0	41.0	3.0	Atelectasis
			Initial Diagnosis of Acute Pulmonary Embolism—Incorrect		
37	7.48	38.5	36.0	2.5	Acute myocardial infarction
38	7.41	38.0	36.0	2.0	Acute myocardial infarction
39	7.46	36.0	34.0	2.0	Acute myocardial infarction
40	7.42	42.0	40.0	2.0	Acute myocardial infarction
41	7.41	41.0	38.0	3.0	Pleuritis
42	7.45	46.0	45.0	1.0	Pleuritis
43	7.47	42.0	40.0	2.0	Pericarditis

The patients without pulmonary embolism whose findings are presented in Tables II and III comprise the controls.

Table IV presents the findings in 16 patients in whom a final diagnosis of pulmonary embolism was established and also indicates the underlying conditions thought to be responsible for the venous thromboses providing the emboli. A very large difference between the pCO_2 of the end-tidal air and that of the arterial blood was present in all of the patients.

TABLE IV.—Acute Pulmonary Embolism—Heart Disease

Pt. No.	*pH*	*$PaCO_2$ mm. Hg*	*$PACO_2$ mm. Hg*	*ΔPCO_2 mm. Hg*	*Underlying disease*
1	7.61	37.5	25.0	12.5	Acute myocardial infarction; thrombophlebitis
2	7.39	33.0	22.0	11.0	Congestive heart failure
3	7.50	37.5	31.0	6.5	Acute myocardial infarction; congestive heart failure
4	7.51	37.0	29.5	7.5	Arteriosclerotic heart disease
5	7.52	40.0	33.0	7.0	Acute myocardial infarction; congestive heart failure
6	7.58	36.0	30.0	6.0	Acute myocardial infarction; congestive heart failure
			Acute Pulmonary Embolus—Postoperative		
7	7.55	36.5	31.0	5.5	Cholecystectomy
8	7.59	39.0	33.0	6.0	Hysterectomy
9	7.52	35.5	29.0	6.5	Bowel resection
10	7.49	30.0	22.0	8.0	Hernioplasty
11	7.48	40.0	30.0	10.0	Gastrectomy
			Acute Pulmonary Embolus—Other Diseases		
12	7.54	36.0	30.0	6.0	Thrombophlebitis
13	7.63	35.0	28.0	7.0	Pelvic abscess
14	7.47	41.0	30.0	11.0	Thrombophlebitis migrans
15	7.48	40.0	22.5	17.5	Thrombophlebitis
16	7.38	36.5	29.5	7.0	Postpartum (1 week)

The means and ranges of pCO_2 values of arterial blood and end-tidal air for the control and acute pulmonary embolism groups are compared in Fig. 1. In the control group the mean pCO_2 values of 38.4 in end-tidal air and 40.3 in arterial blood results in a small mean pCO_2 difference of 1.9 mm. Hg. This contrasts sharply with the mean pCO_2 difference of 8.4 mm. Hg in the pulmonary embolism group. The large difference is due to the very low mean end-tidal air pCO_2 of 28.5 mm. Hg in the presence of a mean arterial pCO_2 of 36.5 mm.

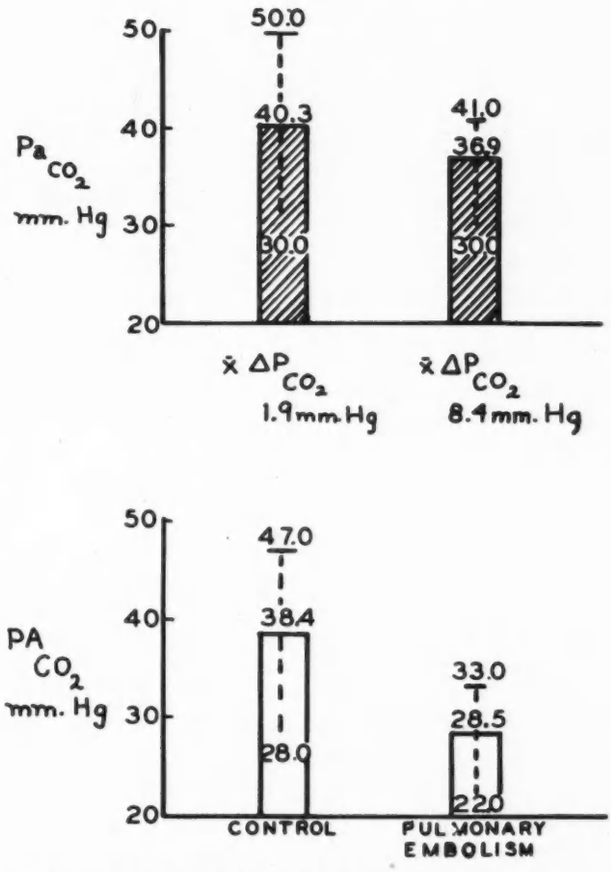

Fig. 1.—A comparison of the range and mean values for the arterial and end-tidal carbon dioxide tensions in controls and in patients with acute pulmonary embolism.

Hg. The latter is only slightly, though significantly, below the normal value obtained in the controls ($P < 0.01$).

The contrast between the pCO_2 differences of the two groups is further illustrated in Fig. 2. The range of 0.5 to 4.5 mm. Hg in the controls does not overlap that of 5.5 to 17.5 mm. Hg in the pulmonary embolism group. The distinction between the two groups would have been even more pronounced if the two patients with pulmonary emphysema and bronchiectasis had been excluded.

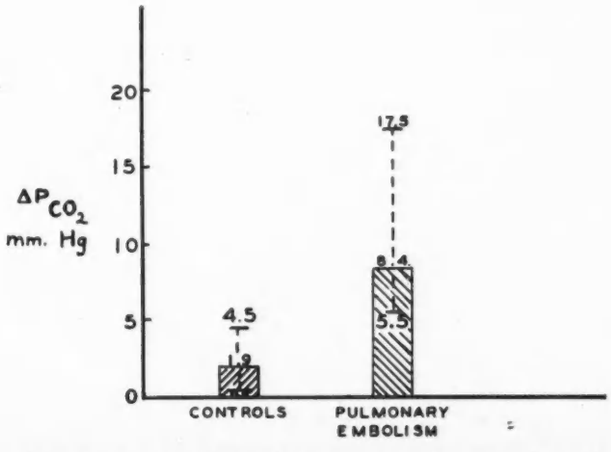

Fig. 2.—A comparison of the range and mean values for the end-tidal air/arterial carbon dioxide tension differences (Δ PCO_2) in controls and in patients with acute pulmonary embolism.

The mean and range of pH in the control group are contrasted with those of the pulmonary embolism group in Fig. 3. The difference between the mean pH 7.44 in the controls and pH 7.52 in the patients with pulmonary embolism is highly significant ($P < 0.01$). Two patients with pulmonary embolism who also had uremia had pH values of 7.38 and 7.39. The range in the remaining patients with pulmonary embolism was 7.48 to 7.63 and the overlap of the control group is slight. The mean plasma bicarbonate in the control group was 26.0 mM/l. as compared to 29.0 mM/l. in the pulmonary embolism group. The difference is statistically significant ($P < 0.01$).

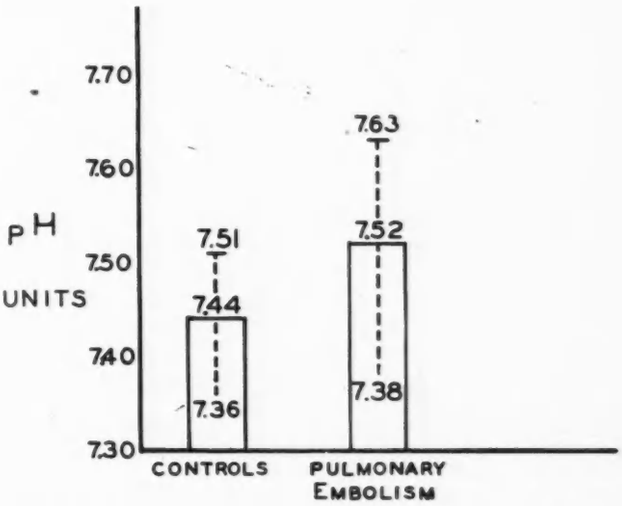

Fig. 3.—The range and mean pH values in control and pulmonary embolism groups.

Table V gives the results obtained in an adult patient studied just prior to and during temporary right main stem pulmonary artery occlusion using a No. 9 ballooned double-lumen catheter, positioned under fluoroscopy. The pre-occlusion end-tidal air and arterial carbon dioxide tensions were 38.0 and 40.0 mm. Hg respectively. The carbon dioxide tensions determined after 3 minutes of complete occlusion by the inflated balloon were 24.0 and 38.0 mm. Hg respectively. The pCO_2 difference increased from 2.0 to 14.0 mm. Hg. The patient's minute ventilation increased from 6.1 to 29.7 l./min. The whole blood pH changed from 7.42 to 7.52 and the plasma bicarbonate from 24.5 mM/l. to 32.0 mM/l.

Discussion

The marked reduction in the end-tidal air pCO_2 and the significant increase in the pCO_2 difference between end-tidal air and arterial blood occurring

TABLE V.—Right Main Stem Pulmonary Artery Occlusion

	Ventilation l./min. BTPS	*HCO_3- mM/l.*	*pH*	*$PaCO_2$ mm. Hg*	*$PACO_2$ mm. Hg*	*ΔPCO_2 mm. Hg*
Pre-occlusion..	6.1	24.5	7.42	40.0	38.0	2.0
During occlusion....	29.7	32.0	7.52	38.0	24.0	14.0

after acute pulmonary embolism are in accord with the observations of other investigators.[11]

A sudden onset of precordial distress and/or dyspnea was the chief complaint in 35 of the patients investigated and provisional clinical diagnosis of acute pulmonary embolism was made in 23 of these. End-tidal air arterial pCO_2 differences of less than 5 mm. Hg were obtained in seven of these 23 patients and a final diagnosis other than acute pulmonary embolism was subsequently established. A pCO_2 difference of at least 5.5 mm. Hg was obtained in the remaining 16 patients. This was in accord with the final diagnosis of acute pulmonary embolism, based on the subsequent course of the disease or necropsy findings. The early clinical diagnostic error was therefore 30%.

The results obtained during experimental pulmonary artery occlusion in a human are in accord with the findings of similar, though more extensive, investigations in dogs. The increase in the end-tidal air/arterial pCO_2 difference which has been recorded during acute pulmonary embolism has been experimentally verified in man. The experiment also shows the rapidity and magnitude of the changes in minute ventilation, pH and plasma bicarbonate which follow pulmonary artery occlusion.

The minute ventilation increased from 6.1 to 29.7 l./min. during the experimental pulmonary artery occlusion, and hyperventilation was observed clinically in 14 patients with acute pulmonary embolism. The increased ventilation cannot be explained on the basis of the raised pH and lowered pCO_2 of arterial blood. Such changes do not result in stimulation of respiration but are expected results of hyperventilation. Sinnott[17] also found that ventilatory changes in cardiopulmonary disease could not be explained by the changes in pH and pCO_2 which occurred. The cause of the hyperventilation has still to be clarified.

The rise in pH in clinical pulmonary embolism and experimental occlusion was only partially explained by a slight fall in the pCO_2 of arterial blood. There was also a rise in plasma bicarbonate concentration. The alkalosis was therefore partially respiratory and partially metabolic. This was of special interest in the individual subjected to experimental occlusion because the plasma bicarbonate rise (7.5 mM/l.) occurred in only three minutes. This was too rapid to be explained by renal adjustment and suggested the possibility of a rapid cation shift from the plasma.

Summary

A study of the dissociation of end-tidal air pCO_2 and arterial blood pCO_2 occurring in acute pulmonary embolism is reported.

The use of the Collins pCO_2 gas analyzer makes possible the determination of end-tidal pCO_2 at the bedside.

The value of this determination in the early diagnosis of pulmonary embolism is indicated.

Experimental right main stem pulmonary artery occlusion in the human produced similar changes.

Increased levels of pH of whole blood of patients with acute pulmonary artery occlusion were found by comparison with those of a control group of hospital patients. The possible cause is discussed.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

The present status of surgery in Canada has been one of gradual evolution from the time when the country was sparsely settled, with no large communities in any one locality, until the present, with our larger centres of population. Formerly, the general practitioner was required to perform operations, and in many parts of the country this must still continue to be the case; but the man who devoted himself solely to surgery was unknown, and though not a few attained well earned reputations as surgeons, yet, under the conditions existing, it is not to be wondered at that few contributions to scientific surgery were made. It can be claimed, however, that our predecessors were always prompt to utilize whatever advantage could be gained by assimilating the ideas of those who in various parts of the world were accomplishing work which made for the advancement of surgery. In this young country, where, in the past, conditions had constantly to be faced which were new and hitherto strange and unusual, our forefathers were dependent upon their own individual effort and were forced to employ new and original methods in the development of the resources of the country. It is, perhaps, something of the inherited spirit of these pioneer settlers which makes it comparatively easy for us to abandon old prejudices; and with less conservatism, perhaps, than that characteristic of the profession in older lands, we are more ready to develop along lines which may be new and revolutionary in character, when once the advantage of such a course becomes apparent. The inspiration for such development has often come to us from without, and, indeed, it is perhaps a characteristic of the Canadian profession that we constantly go abroad to study the methods employed and the work done by our colleagues in other lands. But from whatever source our ideas have been obtained they have been put in force in such fashion and with such discretion that I think we can justly claim that nowhere is work done in surgery with more uniform efficiency than can be found in the various hospitals in Canada today.—A. Primrose: 1911 Address in Surgery to the Canadian Medical Association, *Canad. M. A. J.*, 1: 591, 1911.

A STUDY OF READING DIFFICULTIES IN TORONTO SCHOOL CHILDREN

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PRIMARY dyslexia means a difficulty in learning to recognize the written symbols of language. It could be considered a sensory aphasia affecting the association areas of the visual cortex. The term "primary" rules out reading difficulties based on known factors including deafness, defective vision, low intelligence, emotional disturbance, poor teaching, absenteeism and cerebral damage. If a child in grade 1 to 3 is reading at least one year behind the level of his intellectual ability, he may be said to have dyslexia.

The purpose of this paper is to present the findings of a study on a group of dyslexic Toronto school children. An attempt has been made to assign proper significance to any ocular errors noted in these children. As a control a second group of children of comparable age with large heterophorias at the reading point was investigated, bearing in mind that heterophorias have been associated with reading difficulties.[1-3]

In Toronto schools two reading consultants see all children who are considered by their teachers to be retarded readers. The child's specific reading problems are determined. A careful study of the general health, intelligence, emotional problems and home situation is made in an attempt to elicit secondary factors. The child is then referred to appropriate consultants for further examination.

METHOD

Twenty-two of these dyslexic children were referred for ocular examination at the Toronto Western Hospital. With the help of the orthoptist an ocular examination and orthoptic assessment of each child were carried out.

FINDINGS

These children were all boys. This is consistent with the recorded literature which indicates that 80% to 90% of dyslexic children are boys. The ages were from 8 to 12 years in this series under study. Each was retarded by at least one year in his reading progress, most by two or three years. One child with superior intelligence was retarded five years relative to his intellectual development. The intelligence quotient of these children varied from 90 to 127 on the Otis or Binet-Stanford scales.

Four of the children were obviously emotionally disturbed. Their mothers had been unable to comprehend the nature of their reading problem and were adding to the emotional strain by putting pressure on the children. When protected from these pressures by understanding parents and by special teaching, dyslexic children usually develop much more satisfactorily than could be anticipated from their early failures. By the time the child is seen by the psychologist, however, it is frequently impossible to differentiate primary from secondary emotional problems.[1]

TABLE I.—VISUAL ACUITY AND REFRACTIVE ERRORS IN 22 CASES OF DYSLEXIA

Visual acuity	*Number*
Normal (20/25)	14
Subnormal (both eyes)	6
Subnormal (one eye)	2
Refractive errors	
Emmetropia (error not exceeding —0.50 + 1.50 dioptre)	15
Myopia (over —0.50 dioptre)	1
Hyperopia (over +1.50 dioptre)	2
Astigmatism (over 0.50 dioptre cylinder)	4
High astigmatism (over 2.00 dioptre cylinder)	0

Table I lists the visual acuity and refractive errors of the group. Uncorrected visual acuity was 20/25 or better in both eyes in 14 children. The refractive errors were all of minor degree. Fifteen children were emmetropic, one was myopic, two were hyperopic and four had low degrees of astigmatism, below 2 dioptres. Three were wearing glasses, and spectacles were prescribed for a fourth. The improvement in vision from 20/30 to 20/20, effected with +1.25 dioptre cylinders, had little effect on the reading problem of this child. He was emotionally disturbed both from stress at home and through school failure. The wearing of glasses undoubtedly aggravated his emotional distress. After consultation with both mother and reading teacher, it was advised that the glasses be discarded.

TABLE II.—HETEROPHORIAS IN 22 CASES OF DYSLEXIA

	Number
Orthophoria	14
Exophoria—for near only	2
—for distance only	1
—for both near and distance	1
Esophoria—for near only	0
—for distance only	0
—for both near and distance	2
Mixed esophoria and exophoria	2

The extraocular muscle balance was measured by cover test, Maddox rod, Maddox wing and synoptophore assessment. Table II lists the abnormalities of muscle balance. The heterophorias were mostly minor. Orthophoria was considered to be present if lateral deviations were consistently less than 4 prism dioptres and vertical deviations less than 2 prism dioptres. Fourteen of the 22 children were orthophoric; three had exophoria for near (i.e. measured at 33 cm. distance) of 4 to 6 prism dioptres; and two had esophoria for near of 4 to 6 prism dioptres. No large heterophorias were present and no significant hyperphorias were

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Read at the First Clinical Convention of the University of Toronto Eye Alumni, Toronto, November 18, 1960.

noted. Most of these heterophorias were variable from one measurement to the next.

All of the children tested showed full stereopsis with some amplitude of fusion on the synoptophore and all were normal with the American Optical stereoscopic fly. All had full convergence facility, to 6 cm.

Measurement of ductions was carried out with the synoptophore. The standards of Lyle and Bridgeman were used.[10] The amplitudes of fusion found in the group are listed in Table III. Plus 25 prism dioptres of convergence and minus 6 prism dioptres of divergence were considered minimal normal amplitude. Weakness of convergence was noted in five children, two of these showing weakness of divergence as well. Most of the remaining children showed a high amplitude of fusion, exceeding plus 50 prism dioptres and minus 10 dioptres.

TABLE III.—FUSIONAL AMPLITUDES IN 22 CASES OF DYSLEXIA

	Number
Normal range	15
Convergence less than 25 dioptres	5
Divergence less than 6 dioptres	2

Note: Four cases with convergence deficiencies increased with practice to normal levels.

Electroencephalograms were performed on all of these children. A further report on the interpretation of these findings will be made.

In assessing the significance of small heterophorias in dyslexic children it was interesting to contrast their reading skills with that of a group of children with large heterophorias, measured at 15 inches. Admissions to the Hospital for Sick Children, Toronto, of children with the diagnosis of strabismus were reviewed. Children 8 to 10 years of age with heterophoria for near, admitted in 1958 to 1960, were selected for study. The children who comprised this group represented both public and private admissions and came from Toronto and surrounding localities. All had large heterophorias of 20 to 60 prism dioptres for near and had good vision in both eyes. The school records of six of these children have been obtained along with the teachers' comments regarding their ability. The assessment of reading ability was made by comparison with their grades in other subjects and with class averages.

Five of these six children were below-average readers. Most significant, reading was the only weak subject of four of the six. One very intelligent boy had an A average in all subjects except reading. He was consistently graded C in reading and was assessed as a poor reader by his teacher. Another boy living in a small town was graded poor in reading. Because of his reading problem he was made to repeat grade 4. In other subjects his marks were all A's and B's. Since he was at least one year behind in his reading progress, he was dyslexic. Three of the remaining four children showed a specific reading weakness. One was an average reader. None of these children has been seen by the reading consultant. Thus we do not know if there are any extraocular factors to account for their slow reading progress.

DISCUSSION

In comparing the reading ability of this second group of six children with that of the six dyslexic children with minimal heterophorias of 4 to 6 prism dioptres of lateral deviation, what significance may be attached to heterophoria as a cause of dyslexia? In a study carried out by Park[2] on 133 dyslexic children an incidence of 45% of small heterophorias was found. Nicholls[5] believes that heterophoria has little bearing on reading retardation. He agrees with Goldberg's statement that muscle imbalance does not affect the interpretation of symbols, but may cause fatigue and discourage reading.[4] This conclusion is borne out by the six children with heterophorias of 20 to 60 prism dioptres, four of whom were moderately poor readers and one of whom was dyslexic. They can surely be classed as secondary reading problems. The majority of the frankly dyslexic children, however, were orthophoric. Of the 22 children examined, the five children who had heterophorias of 4 to 6 prism dioptres had borderline orthophoria only.

Goldberg, Marshall and Sims[7] have reported a study of electroencephalograms in dyslexic children. They report a high incidence of electroencephalographic abnormalities, predominantly of the occipitoparietal lobes, and suggest that primary dyslexia may be the result of birth or prenatal anoxia. This may account for some of the unexplained cases of primary dyslexia.[6] However, one cannot ignore the fact that of the 1 to 2% of our school children who are dyslexic, 80% to 90% are boys, and there is a strong incidence of family history. These data are borne out by many studies.

CONCLUSION

The exact nature of so-called "primary" dyslexia is not determined. We know that there are 1000 to 2000 dyslexic children in Toronto. The reading consultants are able to assess 300 of these children every year. Thus, many do not even have the advantage of reading consultation. The oculist may have these children brought to his office in the hope that an ocular error can account for the reading failure and that the reading problem may thus be solved. While heterophorias may result in slight reading retardation, and should be dealt with when symptoms of fatigue or asthenopia are present, stress should not be placed on small ocular errors. It is important that the oculist recognize the real problem and refer the child for proper assessment. His responsibility lies in encouraging a great extension of the special educational facilities available for these children. These children can be taught to read but only in small classes, with specially trained

teachers and by utilizing all methods of learning.[8,9] Until such facilities are available, many intelligent children will continue to experience frustration and much of their talent will be lost.

I wish to thank Dr. Clement McCulloch for his encouragement; Miss Lillian Silva-White, Orthoptist, for her examination of these children; Miss Phyllis Todd, Reading Consultant with the Toronto Board of Education, who made available these dyslexic children and their records; and the Toronto Board of Education.

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CERTAIN MANIFESTATIONS OF RESPIRATION IN PREMATURITY

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THIS study of newly born premature infants attempts to correlate the respiratory rate patterns and the signs of respiratory distress with prognosis for survival.

Infants suffering respiratory distress have been shown to have increased respiratory rates.[1,2] Miller[3-5] emphasized the significance of the trend of the respiratory rate, reporting that cases of respiratory insufficiency and deaths occurred in those whose respiratory rates increased during the first day or two of life. This was in part confirmed by studies[6,7] in which it was noted that most, but not all, of the deaths occurred in such cases. Opposed to this observation are reports[7,8] of deaths from respiratory insufficiency in infants with persistently low rates.

Bauman,[9] using a method of scoring respiratory retractions similar to that used in this study, reported that dyspneic premature infants had a case fatality rate about six times as great as that for those without distress.

METHOD

Observations were made on every infant whose birth weight was between 1000 and 2500 g., admitted to the Premature Nursery, St. Joseph's Hospital, Toronto, from August 1, 1958, to December 31, 1960. Because there was a relatively large number of heavier premature infants, those born during the last six months of this period with a birth weight between 1750 and 2500 g. were excluded.

Respiratory rates were measured for one minute at two-hour intervals for the first 48 hours of life and at four-hour intervals for the next three days. Measurements were not made when infants were crying or feeding. The initial measurement was made during the first hour of life and a very few babies were excluded because this procedure was not carried out.

The degree of respiratory distress was determined by the standards of Silverman and Andersen.[10] One or two points, according to severity, are awarded for each of five signs of respiratory distress: xiphoid retraction, intercostal retraction, retraction of upper chest, chin retraction, and expiratory grunt. The distress score may range from 0, for no distress, to 10, for very marked distress. Distress scores were determined at the same times and intervals as were respiratory rates.

Infants received oxygen only for cyanosis or respiratory distress. Concentrations were kept below 40% unless otherwise ordered by the attending physician.

Deaths occurring in the first seven days were recorded.

Statistical significance of the findings in this study was determined by means of fourfold contingency tables and the chi-square (X^2) test. A probability value (P) of less than 0.01 is considered highly significant.[11]

DEFINITIONS

Respiratory Groups

Infants were allotted to one of three respiratory groups according to the trend of the respiratory rate and approximately by the criteria of Miller and Conklin.[3] A fourth group was added to include those with persistently low rates.

Group I consists of infants whose respiration started at 30 to 50 per minute and was maintained within these limits.

Group II consists of infants whose rates within the first hour were over 50 per minute but subsequently fell to between 30 and 50 per minute.

Group III consists of infants whose rates increased significantly in the first 24 hours to reach a maximum in excess of 50 per minute. An increase in rate was considered significant if two consecutive readings showed an increase of 15 per minute over the rate recorded initially. Thus, to be in-

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cluded in Group III an infant must show both an increase in rate of at least 15 per minute and a maximum rate of over 50 per minute within the first 24 hours of life.

The bradypneic group include those in whom all or most of the rates recorded in the first 24 hours were below 30 per minute.

Distress Scores

Infants were allotted to one of two groups according to the distress score during the first 24 hours.

"No distress" includes those whose score did not exceed 2 in two consecutive determinations.

"Distress" includes those whose score exceeded 2 in two consecutive readings.

OBSERVATIONS

Observations were made on 269 infants. These are divided into heavier and lighter categories according to whether the birth weight was over or under 1750 g.

The respiratory rate trend in relation to incidence of death within seven days is shown in Table I.

TABLE I.—DEATHS IN FIRST SEVEN DAYS IN RELATION TO RESPIRATORY RATE TREND IN FIRST 24 HOURS

Birth weight—1001 to 1750 g.	*Lived*	*Died*	*Total*
Groups I plus II	18	4	22
Group III	26	16	42
Total	44	20	64

$P>0.10$ ($X^2 = 1.8$ with Yates's correction).
Bradypneic group, 13 patients, all of whom died.

Birth weight—1751 to 2500 g.	*Lived*	*Died*	*Total*
Groups I plus II	136	2	138
Group III	32	19	51
Total	168	21	189

$P<0.01$ ($X^2 = 45$ with Yates's correction).
Bradypneic group, 3 patients, all of whom died.

Most of the infants who died were in respiratory Group III; that is, they had an increasing respiratory rate during the first 24 hours. The heavier infants show a highly significant difference in incidence of death between Group III and Groups I and II combined. With the smaller infants this difference is not significant even at the 10% level.

Of the 57 deaths, four were in respiratory Group I and two in Group II. All but one of these six cases had high distress scores. The one exception was a 1300-g. infant whose respiratory rate was maintained at between 40 and 50 per minute, without evidence of distress, until death occurred at 50 hours of age. There was no postmortem examination in this case.

The bradypneic group consists of 16 infants all of whom had severe distress and all of whom died within 20 hours of birth. These babies were considered by the observers to be severely depressed.

The relation between distress score and incidence of death in the first seven days is shown in Table II. Almost all the infants who died suffered respiratory distress as indicated by a high score during the first 24 hours. This is shown to be highly significant for both larger and smaller infants on application of the chi-square test.

TABLE II.—DEATHS IN FIRST SEVEN DAYS IN RELATION TO RESPIRATORY DISTRESS IN FIRST 24 HOURS

Birth weight—1001 to 1750 g.	*Lived*	*Died*	*Total*
No distress	17	1	18
Distress	27	32	59
Total	44	33	77

$P<0.01$ ($X^2 = 11.5$ with Yates's correction).

Birth weight—1751 to 2500 g.	*Lived*	*Died*	*Total*
No distress	136	2	138
Distress	32	22	54
Total	168	24	192

$P<0.01$ ($X^2 = 47$ with Yates's correction).

The incidence of distress in the various respiratory rate groups is shown in Table III. Respiratory distress occurred in 5% of cases in Group I, 28% of cases in Group II, 76% of cases in Group III, and 100% of those in the bradypneic group.

TABLE III.—INCIDENCE OF RESPIRATORY DISTRESS IN FIRST 24 HOURS IN VARIOUS RESPIRATORY GROUPS ALL PATIENTS WEIGHED 1001 TO 2500 G.

Respiratory group	*No distress*	*Distress*	*Total*
I	78	4	82
II	56	22	78
III	22	71	93
Bradypneic	0	16	16

Postmortem examinations were performed on 43 of the 57 infants who died. The findings are summarized in Table IV under what was considered the principal cause of death in each case. "Other conditions" includes infections other than pneumonia, severe congenital anomalies, and three cases in which the cause of death was not determined. Pulmonary lesions were the principal abnormality in over two-thirds of the cases and, of these, almost two-thirds showed marked hyaline membrane formation.

All infants with pulmonary hyaline membrane disease, except for one who also had an intrapulmonary hemorrhage, died within 25 hours after birth.

Evidence of infection was detected in six infants at postmortem examination. In four of these it was determined that the mothers' membranes had ruptured within one hour prior to delivery. In two cases with bronchopneumonia, in which death occurred before the age of 12 hours, the membranes had ruptured at least three days before delivery.

TABLE IV.—POSTMORTEM DIAGNOSIS IN RELATION TO RESPIRATORY MANIFESTATIONS IN FIRST 24 HOURS

Postmortem diagnosis	*Total cases*	*Number in each respiratory group*				*Respiratory distress*	
		Group I	*Group II*	*Group III*	*Bradypneic*	*Absent*	*Present*
Hyaline membrane disease alone	15	2	2	9	2	0	15
Hyaline membrane disease with bronchopneumonia or intrapulmonary hemorrhage	3	0	0	3	0	0	3
Bronchopneumonia alone	3	0	0	2	1	1	2
Intrapulmonary hemorrhage alone	3	0	0	3	0	0	3
Massive pulmonary aspiration	5	0	0	4	1	0	5
Intracranial hemorrhage	7	1	0	1	5	0	7
Other conditions	7	0	0	3	4	0	7
	43	3	2	25	13	1	42

The greatest incidence of bradypnea occurred in those with intracranial hemorrhage.

Seventy-three per cent of deaths in the 1001 to 1750 g. weight group and 42% of those in the 1751 to 2500 g. group occurred in the first 24 hours.

DISCUSSION

Of all the infants studied, 4% of those in respiratory groups I and II combined died within the first seven days, 38% of those in Group III died, and 100% of the bradypneic group died. The prognostic significance of this in the case of infants of lighter birth weight (1001 to 1750 g.) is diminished by the fact that a majority of those who survived also fell in Group III.

The Group I pattern of respiratory rates seems to be normal for well premature infants. The Group II pattern was associated with a higher incidence of distress, but not of death, than the Group I pattern. Miller *et al.*,[12] as a result of their studies of pulmonary function, report that a Group II pattern warrants a diagnosis of mild respiratory insufficiency. However, it seems to be a fairly benign type of respiration.

In contrast, the Group III pattern occurred in most of the smaller premature infants, and in most of those, both smaller and larger, who died. It was also associated with a high incidence of respiratory distress.

The bradypneic group all appeared to be severely depressed, all had respiratory distress, and all died.

Measurements of the degree of dyspnea during the first 24 hours by means of a distress score indicate that 2% of the infants without distress and 48% of those with distress died within the first seven days. Distress was more common in the smaller infants and, of these, over half of those with distress died. The heavier infants were better able to overcome their dyspnea; approximately 60% of those with high distress scores survived.

These data indicate the value of frequent observations of respiratory rates and distress scores during the first day or two of life in the premature.

Forty-two of the patients coming to postmortem examination had high distress scores during the first 24 hours. Fourteen of these had no demonstrable pulmonary lesions, and in all but three of these death was definitely due to lesions in other organs. Thus a clinical diagnosis of the respiratory distress syndrome of the newborn can result from disease not primarily affecting the lungs.

The opinion of Bowden, Goodfellow and Snelling[13] that in some instances premature rupture of the mother's membranes may predispose to intrauterine infection was supported in our series by the early death of two infants from bronchopneumonia.

SUMMARY

Almost all premature infants whose respiration started at 30 to 50 per minute and was maintained at that rate, and almost all those with rates which were initially high but subsequently fell to within these limits, survived the first week of life.

Although most of the infants who had a rising respiratory rate within the first 24 hours survived, most of the deaths occurred in this group.

Prolonged bradypnea within the first 24 hours was accompanied by respiratory distress and followed by death in all cases.

Very few of the infants who had neither a rising respiratory rate nor bradypnea died.

A high respiratory distress score within the first 24 hours was followed by death in 48% of cases. The remaining 52% of those with respiratory distress recovered without specific treatment other than the usual control of environmental temperature, humidity and oxygen.

Almost one-third of cases of the respiratory distress syndrome were shown at postmortem examination to be due to lesions elsewhere than in the lungs.

Smaller infants had a higher incidence of abnormal respiratory rate trends and a higher incidence of respiratory distress, and died more frequently and at an earlier age than heavier infants.

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MEDICAL ECONOMICS

GOVERNMENT AND MEDICINE*

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"GOVERNMENT and Medicine" was the title which your President suggested for this talk. The assumption was, I suppose, that the common ground is finance and medical economics, matters that most busy doctors like to ignore if they can. But some form of government assistance to the people in regard to the costs of medical care is inevitable in these days of social consciousness. Increased assistance to medical education should be equally inevitable.

At the outset, let me make the claim that nowhere in the world is the level of medical practice generally superior to that in Canada today. In most areas it is far below Canada's standards. The poor patients have rarely been forgotten by our hospitals, and doctors do care for a significant proportion of patients free of charge. The present situation can be made worse by legislation. It can also be vastly improved.

In the common ground that lies between Government and Medicine, economists should face two problems:

A. What plan should be devised to help people of lower income face the mounting medical costs?

B. What plan should be introduced to support medical education and the rising hospital costs?

Medicine in Canada is passing through a period of reconstruction as the government of one province after another discovers in it a popular avenue of public service. Premier Douglas reassured the members of the medical profession in Alberta‡ in regard to government financing with these words: "The only change is that the doctor will send his account to the Government instead of the patient!"

Here is a simplification of the whole affair! But is it as simple as all that? It should make the patient very happy, the rich one as well as the poor, provided he does not lose thoughtful, friendly contact with his physician. No one wants to become a number on a card, whose medical case is reviewed by anyone who happens to be on duty. It should please the physician, if, while bringing his family a reasonable living, the scheme does not lose for him the ancient "doctor-patient relationship" or the opportunity to move forward in the art of the practice of medicine. The thoughtful voter might well be pleased, too, provided the total cost of medical care is not doubled without an improved level of service. These are important provisos which call for decision before drastic action is taken.

National health insurance is an excellent scheme. This has been obvious ever since it made its first appearance on the socialistic horizon in prewar Germany. After the First World War, it helped the British people to meet a serious economic emergency when Lloyd George introduced it there and Bevan finally applied it as a part of the provisions of a welfare state.

I have watched the change that it brought to Great Britain through the years, as a medical student before socialization and later while on frequent visits to that country. I would agree with Dr. Murray Stalker, who is a champion of the cause of more effective medical service by general practitioners. He has expressed the opinion[1] that socialization in Britain has brought improvement in the general level of hospital and consultant service but has produced an opposite effect upon the equally important service to the public by the general practitioners.

Furthermore, my conclusion is that unnecessary treatments are more frequent under their socialized system and hospital workers lazier and less productive, causing great increase in the total cost of hospital care.

I suspect, too, from my own observation, that the increasing dependence of the medical schools of Great Britain on federal support, and on central control, has had an unfortunate effect on academic initiative. It has probably decreased the total scientific achievement that would have been forthcoming under a system of support which left the universities greater independence and freedom.

Of course there may be other reasons that would explain the comparatively more rapid improvement in medical science in Canada. Such judgments of another country may easily be in error and comparisons are often difficult. Nevertheless, we must make such judgments and such comparisons, since the time has come, it seems, for our social reform. Comparison may help us to avoid certain pitfalls.

Society has taken into its own hands the reorganization of medical practice for the benefit of the voter. And all voters are potential patients and the members of voters' families as well. They will all fall into our hands eventually, even cabinet ministers and social reformers.

In the book of Ecclesiasticus it is written: "He that sinneth against his Maker, let him fall into the hand of the physician." Here was a warning to potential patients and obvious contempt for the practitioner. But it was also written: "Honour a physician with the honour due to him for the uses which ye may have of him: for the Lord hath created him."

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*Address to the 94th Annual Meeting of the Canadian Medical Association, Montreal, June 23, 1961.
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‡An address to the Edmonton Academy of Medicine, December 7, 1960. (See *Alberta M. Bull.*, **26**: 22, 1961.)

Physicians today are not what they were in ancient Israel, fortunately, and sin is no longer listed as a cause of disease even in the wordiest of the books on pathology. Though perhaps it should be! We physicians watch intemperance and lack of discipline wreck so many lives! Physicians might do well to accept sin again as a cause of disease—sin against the laws of health and good behaviour. Sin might even be classified under the heading of pathology and enlarged into a department of preventive medicine. But, fortunately for you and for me, the topic of this talk is Government and Medicine, not sin.

We in the medical profession realize how grateful we should be to those in public life who are willing to struggle now with medical economics in this and in every other province of Canada. Representatives of the Government and of the organized medical profession should negotiate, as J. H. MacDermot[2] has urged, with "calmness, patience and even generosity". There is so much that might be lost by hasty legislation, so much to gain from wisdom.

Let no well-meaning leader of any political party suppose that good doctors can be paid and directed as simply as road builders and civil servants. From the beginning of reputable medical practice, the doctor has charged a fee to those who could afford it; but he has never taken orders from the member of that family who might, or might not, pay the fee when the work is over. He does what he believes to be best for the patient, according to his years of study. He can be discharged by the patient or the head of the family, but he cannot be directed. He is responsible to a higher authority and to a religion of medicine which has come down to him from Hippocrates. A good physician will always put this above the authority of paymasters in or out of the State.

E. P. Scarlett[3] of Calgary wrote once that it is our mission, in the profession of medicine, to prescribe "for the mind and the soul in perilous times". These are perilous times. Politicians and medical administrators would do well to examine carefully the ways of this ancient profession before they recommend legislation. Consider what Medicine has done for the world with no more than academic organization. Economics and Science, when added together, make a sum that falls far short of what Medicine is. Let me look back for a moment.

Compassion led the caveman's woman to comfort her weeping child, and to dress the wounds of her man when he crawled home hurt from the hunt. After the curtain of history rose on the civilization of Mesopotamia and Egypt and Israel we get glimpses of the art of Medicine as it took form slowly, strangely, blocked as it was by religious superstition. By the fifth century B.C., the lights of intellectual advance were burning in the ancient kingdoms, but the light was low indeed, and we must turn to the tiny Greek island of Cos in the Eastern Mediterranean to discover the birthplace of modern medicine. Hippocrates practised there and headed a small group of Asclepiad physicians. There can be no doubt of his leadership. Socrates, Plato and Aristotle all considered him the greatest practitioner and medical teacher of his time.[4]

There is no place in Medicine, he declared, for religious superstition or for "the unprovable hypotheses of the philosophers." Neither devil nor god enters the body of man to plague him with disease. The physician should study nature and the way of the human body as it reacts to each disease so that treatment may be planned to support the patient and aid natural recovery.

But Hippocrates, though he defined the rules of science and defended the "Art of Medicine" against priest and philosopher, did not leave physicians to an atheistic negativism after the manner of some materialistic thinkers of the last hundred years. In the belief of Hippocrates, the gods had ordained the working of nature. The physician, then, should learn these ordained ways without calling on the gods to change their laws by miraculous interference. He went beyond this, and gave his disciples an oath which put into words the compassion and the dedication to the good of the sick which has always been instinctive in the hearts of those who are drawn to the Art of Medicine. Call it humanism if you like, or compassion or *religio medicinae*, but do not let it be lost amidst the modern preoccupations with science and administration and economics.

About four hundred and fifty years after Hippocrates composed his oath, Christ told the parable of the Good Samaritan. It was a splendid illustration of compassion, but it was compassion without science. To find the two united, after Hippocrates, we turn the pages of history and read with disappointment of the persistence of superstition, the belief in evil spirits, miraculous healing of the "royal touch", and in time, blind belief in the authority and wisdom of the "Professor."

If time permitted, I would trace the evolution of science in modern medicine by describing the labours of Paré and Harvey and Hunter and Lister. They cleared the way for the flowering of science in modern medicine. And Darwin led a crusade to free biology from religious superstition. You might prefer to select other heroes. There are many of them and they played important roles in the approach to this new era of civilization. When at last the stage had been set by freedom of thought, and when the driving force of medical curiosity was no longer held in check by false prejudice—when new thinking and discovery were viewed by society as praiseworthy virtues, then medical men, equipped with the experimental method as well as the Hippocratic technique of observation, created modern medicine in one century of advance. It might seem a blessed miracle, but it was something quite different from the miraculous, something far more permanent. It was based on fact and reason.

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There is a divine plan—no doubt of that—in the working of disease, in the reactions of the body, and in the inter-relationships of the physical universe. These are things for us to study and to deal with on a logical basis. But medicine is not purely a science of the inanimate, like physics. It is an art that deals with men and women, their hopes and fears and happiness. We must study the human mind and we must take thought of the destiny of man and his relation to God.

But I must turn back to the middle ground of economics. I should try to describe Modern Medicine in specific terms, hoping that Government will contribute to its strength, not to its weaknesses. Medical education and medical practice must be taken as a whole, since medical practitioners cannot, or should not, be separated today from the teaching and consulting centres. Let me refer to the whole complex under the title of *University Medicine*. In some cases large hospitals or medical clinics, not directly included in the teaching scheme of a medical school, may nevertheless undertake many of the functions that I shall include in the concept of University Medicine. All of these hospital centres should have their active lines of communication radiating out to the surrounding practitioners, and all good hospitals should have intimate communication with a central medical school for purposes of consultation.

Today there is, in most large centres of population around the world, a university and a university medical school, and teaching hospitals most intimately related to it for the purposes of University Medicine. It may be taken as axiomatic that centres of University Medicine, whatever their structure, should be organized with a triple objective in view: (a) the treatment of diseases, especially the more difficult ones, (b) the teaching of medicine, and (c) medical research. Good teachers and good practitioners must either take part in current research or have continuous contact with it. No teaching institution can be considered first-rate if research is omitted. All these things, however, must be kept in due proportion—practice, teaching, investigation.

The recent suggestion that any hospital should pay for legal and political service comes as a shock to me. If hospitals are charitable organizations, why should these services not be contributed to this good cause free? What better public service can there be?

Now let us look at a centre of University Medicine from the point of view of the community that supports it. What should people hope for and what should they be willing to pay for? They should hope for a unit so organized in its practice and teaching that it serves the best interest of the local patient, the local student, and the medical man who is practising in the district outside the medical school. There is nothing very new in that statement of objectives except that the outside practitioner is sometimes forgotten. There is indeed nothing new in anything that I shall say. But there are things sometimes forgotten and often ignored.

Medicine means many things to many men. "*Quot homines, tot sententiae.*"[5] Even for physicians medicine has many sides. Some who practise may forget the meaning of the art, considering too much their personal gain and professional reputation. Some who work in laboratories may never see a patient; and if they actually forget him, they can hardly be said to practise the art. Others see the art in broad perspective. They place the doctor-patient relationship first and they strive to learn and to investigate while earning enough for a reasonable living. They would, if they could, follow the old Greek maxim, "nothing in excess, all things in due proportion." But the organization of University Medicine may fail to make this possible.

Among the laity, too, medicine has many connotations and their consideration varies from awe to contempt. Most people expect of us doctors two things above all, skill and compassion. They will forgive us many things, including honest mistakes—and God knows there are things to be forgiven! But one thing they will never forgive. That is the loss of compassion for those who suffer. They know, and we know, that it is the wellspring of our art.

I have had a varied experience in surgery and science, having studied under distinguished teachers and having worked in, or visited, many universities and hospitals. I had the almost incredibly good fortune to plan an academic department with complete co-operation from McGill University and the hospitals in Montreal, and with support from foundations, generous citizens and Provincial and City governments. I watched the building of a clinical institute, and after its doors opened, took part in its operation for more than a quarter-century. I saw it endowed permanently for scientific work and staffed for the treatment of diseases of the nervous system and for teaching and research.

But in the outset of my career, I faced most of the fortunes that come to doctors. I had to borrow money for a time to support our family while completing graduate study. I have practised surgery with no university salary, using an outside office, and I have been on a "full-time" university salary, and on no salary with private and public practice facilities within a university hospital. I have had salary supplemented by practice within the hospital and a ceiling on the practice income. This is an excellent scheme.

After all, if a man has patients and colleagues and students and space and good will, no profession can give him more thrills, more solid satisfaction and more long hours of absorbing toil than academic medicine.

One definite conclusion I might draw: If the ability of the staff is reasonably good and the spirit is right, almost any system can be made to work quite well, although I must add that some schemes are vastly worse than others or, should I say, some are vastly better! High morale in any university,

or in any scientific or clinical group, will develop if there is unselfishness at the top. Without high morale among doctors and nurses, so many opportunities are missed! My advice to Deans and hospital boards would be this. Select for your chiefs of staff those who will put the patient first, and those to whom young men are truly loyal. Do not allow yourselves to be bound by the chains of a progressive seniority system, or dazzled by self-seeking brilliance in our profession.

There are certain conditional demands that could fairly be made of the ideal unit of University Medicine. Physicians and surgeons on the hospital staffs should be able to maintain a normal "doctor-patient" relationship with all that this means in terms of friendship and sympathy. The staff men should admit patients to hospital from consulting room and public dispensary and, if they have cared for them in hospital, they should have facilities to follow-up the cases that are medically or scientifically important in a personal way. They should do this without depriving the referring practitioner of his interest in and responsibility for the patient.

All active physicians and surgeons on the staff should follow some particular interest in clinic or laboratory and take part in staff conferences. There should be on the staff a due proportion of clinicians who practise on a "geographical full-time scheme". This should mean that they can spend most of their time in hospital, laboratory and classroom and still support themselves and their families at a reasonable level. If they do not want to spend most of their time there, perhaps they are not the proper men for those posts and should be replaced. No absolute rules of time here and time there should be necessary. Laboratory men should have contact with their patients whenever possible, in connection with their specialty. Subjects for research should most often be dictated by the problems the patients bring to the clinic.

In the teaching of undergraduates there should be no undue emphasis on research at the outset, but each student should be made to realize that final authority is to be found in the nature of body processes, not in professional pronouncements. The student must discover that authority and truth are in bed with the patient.

The modern practitioner's job is increasingly difficult, and increasingly important. Most patients are best treated at home or in outside offices and clinics. Here is an axiom of policy in my opinion. If the people in the community are to be well served, an effective give-and-take between outside practitioners and doctors on the university staffs is essential. The national and international societies and congresses, which serve to keep specialists abreast of general advance, should be matched by general practitioner societies to keep the generalists abreast of the opportunities of medicine. And there should be recurring short revision courses for them in the University Hospitals. With proper organization, the practitioner can always serve as the intermediary and the wise arbiter between family and hospitals. Only he can bring to an end the present unsatisfactory and often blundering efforts of patients to find the proper specialist.

The community, which benefits from a centre of University Medicine and is willing to support it, has a right to expect this interrelationship with the practitioners. But what else has the public the right to expect? Care of patients, training of young physicians, leadership in matters of public health and a well-earned reputation for excellence.

Beyond that, neither the public nor the government should go except in emergency. They would be unwise to intrude or to presume to pass judgment on medical affairs. The internal organization of teaching and research and practice is a matter for university decision and for local professional initiative.

In conclusion, Medicine is an institution as ancient and as honourable in its service to humanity as democratic Government. It will continue to serve best if allowed its independence. Give Medical Education adequate support so that science can continue to develop and to contribute to the health of the nation. Give the people such insurance that they can meet the emergencies of major medical expense. Give the hospitals such assistance as is necessary for them to carry on, with due economies. But never make medical service completely free. That would, in my opinion, increase the total cost to the taxpayer without providing more efficient care. It would lose to the individual patient the direct friendly guidance and counsel of a personal doctor.

Completely socialized medicine is obviously better than nothing for a nation of citizens whose income is at a bare subsistence level. But Canada is not that. Our present medical service is by comparison excellent, although we could improve it vastly. Science and public dispensaries are not enough. Let our efforts be directed toward bringing the general practitioner and the family doctor back into a position of strategic importance. Let us improve the communication between him and the great modern hospitals. This is what is needed to supplement the advancing specialty organization of major hospitals. Let us begin to support research, teaching, and the consultative centres at a higher level than other countries, not lag behind as at present.

If its dignity and independence are preserved, Medicine may play a most important role, fulfilling its destiny through the storms of the century that lies ahead. The science of the body of man and its diseases make up only half of the field in which we can serve mankind. It is clear that in the middle ground of economics that lies between Medicine and Government in each Province, momentous decisions are being made. Look carefully then; see Medicine as it is and how it could be changed for better or worse. And in the years to come it may be

truly said: *"Wisdom hath builded her house, she hath hewn out her seven pillars."*

The physician, too, "is worthy of his hire". Beyond that, the responsibility is ours to see that all men, when they are patients, learn the meaning of compassion as well as the science of medicine. Whatever happens and however society may be reorganized, we will continue to serve the sick according to the high tradition of our art, putting his good before all else, guarding his secrets, understanding him, and guiding him as best we can.

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SPECIAL ARTICLE

AN ASSESSMENT OF RESEARCH METHODS REPORTED IN 103 SCIENTIFIC ARTICLES FROM TWO CANADIAN MEDICAL JOURNALS

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RECENTLY, four articles[1-4] dealing with techniques of statistical analysis and the design of experiments have been published in this journal. The purpose of this paper is to apply some of the methodological implications of these articles to an assessment of the research techniques used in 103 studies reported in the *Canadian Medical Association Journal* and the *Canadian Journal of Public Health*. This paper is not an analysis of the content of medical experiments but it is rather an evaluation of their methodological design.

This distinction between contents and design was made in 1937 by A. Bradford Hill in the Preface to the first edition of his text, "Principles of Medical Statistics".

"Statistics are curious things. They afford one of the few examples in which the use, or abuse, of mathematical methods tends to induce a strong emotional reaction in non-mathematical minds. This is because statisticians apply, to problems in which we are interested, a technique which we do not understand. It is exasperating, when we have studied a problem by methods that we have spent laborious years in mastering, to find our conclusions questioned, and perhaps refuted, by someone who could not have made the observations himself. It requires more equanimity than most of us possess to acknowledge that the fault is in ourselves."[5]

The studies which are analyzed in this paper were originally selected to provide illustrative data for seminars to be given to third-year medical students. During the academic year 1961-1962 these seminars on methodology will precede the Third-Year Project which is one phase of the third-year course presented by this department.[6, 7] This project involves students in the preparation of comprehensive reports focusing on specific diseases. Among other questions dealing with their topics, students are asked to consider the following points:

"1. In the course of your investigation you will have read many studies relevant to this disease. Criticize the methodology used in those studies.

"2. It is unlikely that you will have been able to find completely satisfactory answers to all the questions dealt with in this Project. In one area which you consider to be inadequately covered by present knowledge you are asked to make specific suggestions for the design of research to fill the gaps."

To date, students have been guided informally by tutors in answering these questions. During the next academic year the tutorial sessions will be complemented by seminars focusing on five aspects of the design of studies using group data. These five points provide the basis for the evaluation of the 103 studies which are analyzed in this paper.

Specifically, the questions posed concern (1) how terms are defined, (2) the selection of the population or the sample of cases described, (3) the use or non-use of control groups, (4) the statistical techniques used in the analysis of data, and (5) the derivation of conclusions.

MATERIALS AND METHOD

All articles published in the *Canadian Medical Association Journal* and the *Canadian Journal of Public Health* from January 2, 1960 to July 2, 1960 inclusive were surveyed. The criterion for the selection of the articles analyzed herein was whether authors used or did not use group data in reporting original research. Consequently, case reports, reviews, descriptive papers and articles providing a survey of the literature on a given topic were omitted from the study. The remaining 103 articles, all of which used group data, were either epidemiological surveys or clinical trials of drugs and descriptions of therapeutic procedures.

The following questions were applied to each article included in the study.

1. Are the terms defined in such a way that it is possible to replicate the study?

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2. Who (or what) does the population (or sample) being studied represent? Are the criteria given by which cases were selected or rejected?

3. What type of control group was used in the study?

4. If the results were not analyzed statistically, could statistical analysis have provided additional descriptive and analytical measures?

5. Are the generalizations induced in the conclusions of the study limited to the findings of the study?

FINDINGS

1. *Definition of Terms*

Systems of classification and the terms used in a study should be defined precisely and should be appropriate to the problem under analysis.[8] In addition to these criteria Fletcher and Oldham[9] note that "Having ensured that the terms in which the diagnosis is to be defined are appropriate and clear and that any system of classification to be used is consistent and comprehensive, it is still necessary to ensure that the individual diagnostic criteria or tests which are to be employed satisfy certain other requirements. They must be repeatable, valid, discriminating and as simple as possible."

In this study the terms or systems of classification used were not explicit in 18 (17.5%) of the articles. Listed below are a few examples of terms or systems of classification for which no other criteria were provided.

1. Normal or acceptable patients.

2. The progress of patients being classified as: excellent, good, fair, poor, and no progress; or, as slight, moderate and complete improvement.

3. Characteristics of patients as being moody, apathetic, content, antisocial, co-operative, alert, adjusted, confused and stimulated.

On the basis of the terms or classificatory systems used in these 18 articles, it is neither possible to repeat these studies in other settings nor for a reader to determine what criteria were subsumed in these categories.

2. *Selection of Samples*

Fisher[10] contends that the process of inductive inference is the only one by which new information is brought into the world. The process of induction (deriving conclusions from the particular to the general) is the basic assumption underlying all sampling techniques. Given certain conditions, it is legitimate in parametric research to draw inferences from a sample to a population. When units of analysis are being selected or a sample is being drawn from a population, the following conditions should be met.[11]

1. The characteristics of the population under analysis are explicitly delineated. It is assumed that these characteristics follow a normal distribution curve in the population.

2. The unit of analysis is specified.

3. The procedure followed in the selection of the sample is described. It is assumed that the attributes of the sample which is selected are representative of the attributes found in the population.

If the above assumptions and procedures have been followed in the selection of a sample, then two additional steps are feasible.

4. From quantitative analysis of the sample, estimates are made of the distribution of specified attributes in the population. The reliability of these estimates is calculated and presented.

5. Hypotheses about the population are tested from estimates of attributes in the population. On the basis of the accuracy or reliability of these estimates, the hypotheses are accepted or rejected (at a prespecified level of significance).

Articles in this study were grouped into three categories. Articles which met the first three criteria were designated as employing "good sampling" techniques. "Inadequate sampling" covered those studies in which samples of cases were used but which did not meet the first three criteria. The category "inapplicable" included (1) descriptive studies, (2) studies in which a total population was used, and (3) reports of small numbers of unusual cases where sampling would not have been feasible.

Using the above criteria, the following results were obtained in this study:

Good sampling	10.8%
Inadequate sampling	41.9%
Inapplicable	47.3%

Several articles classified here as having inadequate samples omitted a description of one or more of the following points: (1) the population from which the sample was drawn or what the sample represented; (2) the time span involved, or (3) the techniques used in the process of sample selection. In two articles the size of the samples being studied was omitted. Several studies, which otherwise met the criteria for good sampling, omitted the reasons why cases were subsequently dropped from the sample. In four articles samples were composed of "unselected cases" or patients were chosen "on the grounds of common sense", without additional criteria being specified.

On the basis of the information provided, it would be impossible to replicate most of these studies with inadequate samples. Also, it would be difficult in these studies to draw reliable conclusions from the groups studied to the specific populations concerned, i.e. from patients with a certain disease to all patients with that disease.

3. *Control Groups*

Several authors in this study equated the inclusion of detailed clinical observations in their reports to the use of control groups. These two facets of research are not identical. The former should be a prerequisite in all research activity. Control groups provide the constants or known variables with which unknown variables may be compared. When a procedure or a therapy is being used for the first time or is being given a clinical trial, it is crucial to know not only the effects on the cases or patients who have been treated but also how these patients differ from those who have not received comparable therapy. Essentially, the use of a control group in an experiment provides the researcher with a basis of comparison of the unknown as gauged by the known.

O. B. Ross,[12] a physician, concluded from his analysis in 1951 of 100 randomly selected experiments that in only 27% of the articles were adequate controls used. Ross's criteria for the use or non-use of control groups were followed in this study.

"The articles were classified as: those which used adequate controls; those which used inadequate controls only; those which used no controls, and those which by nature precluded controls. A satisfactory control was defined as a number of untreated patients, or procedures, approximately equal to the number treated, with the specific form of therapy being tested as the only variable factor. Controls that were held to be inadequate were those in which the number of untreated patients was too small, or a different time or place or other variables were utilized in comparing the treated and the controls, or controls were not subjected to the same physical or emotional conditions as those treated (injections and roentgen radiation). Use of controls was held to be impossible when there were reported small numbers of unusual cases in which the use of controls obviously could not have been expected or when the severity of the disease was such that none should be left untreated."[13]

In this study the category "control impossible" was extended to include descriptive and epidemiological surveys where the use of control groups was inapplicable.

The results of this study of 103 articles were:

No control	35.5%
Inadequate control	12.5%
Well controlled	25.1%
Control impossible or inapplicable	26.9%

These results, as do those of Ross,[12] highlight the need for careful planning in the development of research design. The absence or inadequate use of controls does not mean that the studies concerned may not have elucidated specific clinical problems. Rather, it is suggested that the findings of 48% (no control and inadequate control) of the articles in this study would have been more reliable, or the conclusions possibly altered, had adequate control measures been used.

4. *Statistical Techniques*

Biostatistics and methodology are the warp and woof of quantitative medical research. These two techniques complement one another in formulating research problems, in postulating and testing hypotheses and in deriving conclusions. While the content of an experiment or of a study using group data may vary, the form, regardless of content, may be assessed by a few generally accepted logical principles. These principles pertain to the organization or logical structure of a study and the statistical techniques used in the analysis of its data. Since the area of statistical theory and techniques is extensive, no attempt is made here to offer a comprehensive statistical assessment of the articles under review.

The articles in this study were assigned to one of three categories. Studies which adhered to accepted principles of statistical argument and design were classified as using "appropriate statistical analysis". Studies which deviated from the above principles were designated as employing "inappropriate statistical analysis". The distinction between "appropriate" and "inappropriate" statistical analysis is described in the discussion of the results obtained in the latter category. Finally, the third category, "additional analysis required", encompassed those studies which reported on group data but in which no descriptive statistical measures were used.

The following results were obtained:

Appropriate statistical analysis	42.7%
Inappropriate statistical analysis	24.3%
Additional analysis required	33.0%

Under the category of additional analysis required, there were 11 articles which presented raw, ungrouped data and 23 articles which used grouped data. None of these studies used descriptive statistical indices. The use of such indices can assist the researcher in deriving his conclusions and can provide the reader with a brief statement of the findings. For example, in one study which described the use of a new drug on over 100 patients, the reader was required to derive his own calculations to assess the average effect of this therapy on different types of patients. The use of measures of central tendency (mean, mode, median) and of deviation would have provided useful summary indices of all the cases in this study.

It is suggested that if descriptive statistical techniques had been used in these 34 articles where no summary indices were employed, then the data might have been presented more efficiently, and

possibly more effectively, than in the absence of such summary measures.

Twenty-five articles (24.3%) were classified as using statistical techniques inappropriately in the analysis of group data. These were studies where (1) the data were internally inconsistent, (2) the definitions of incidence and prevalence were confused, (3) several levels of significance were followed, and (4) the techniques of association were only partially used.

The data in four articles were internally inconsistent, i.e. the findings in the tables or in the descriptive reports did not tally with the totals presented. For example, in one study seven cases were dropped from the analysis. The remaining 96 cases were described, but the total number of cases initially under analysis was listed as 112 individuals. Thus no information was presented on nine cases.

In five articles the concepts of incidence and prevalence were either confused for one another or misused. The concept of incidence refers to the number of cases *arising de novo* in a specified population within a given time interval. In contrast, prevalence refers to the number of cases *existing* in a specified population at or over a given period of time. Two authors reported the incidence of cases in given diseases while actually describing the concept of prevalence in their studies. No time interval was specified in two studies and in one instance the total population under consideration was not given.

When tests of statistical probability (e.g. t-test, chi-square) are used in a study, the results are usually expressed in terms of a prespecified level of significance (e.g. .05, .01). Although the selection of a given level of significance is arbitrary, it is usual to specify it before the results are analyzed and to follow this level of significance consistently in the interpretation of the results. If the level of significance is changed to suit the data throughout the course of a study, then no consistent pattern is established for the acceptance or rejection of the hypotheses. Three articles in this study used various levels of significance in reporting their findings. An example illustrates the confusion which this situation may engender. In one study 13 different levels of significance were cited (e.g. 0.1, 0.2, .05, .01, .001) in using the t-test (testing the significance of the difference between means). When the authors of this article subsequently concluded that their findings were statistically significant, it was impossible to ascertain to which of the 13 levels of significance reference was being made.

Thirteen articles evinced confusion in the use and interpretation of the concepts of relationship (e.g. contingency, analysis of variance and correlation). In four articles authors reported that there was a significant correlation between two variables and in each instance one of the variables had not been described. In nine articles authors established the relationship between variables by using bargrams, scattergrams and graphs. Although pictorial evidence is useful, it is not a substitute for the more precise coefficients of association which could complement these findings. Statistical techniques have been devised to measure the existence, direction and degree of association between two or more characteristics. The use of such techniques (e.g. Q, r) would yield more concise statements of association than the conclusions based solely on pictorial data in which "close" or "significant" correlations were reported.

5. *Derivation of Conclusions*

Although conceptually there are different approaches to the nature of statistical inference, there is some agreement in practice about several of the common difficulties which should be avoided in research studies. These difficulties and the rules of statistical inference have been thoroughly outlined in several reports.[14-17] Only three types of conclusions which may be questioned on the basis of logical inference are examined here.

1. Conclusions drawn to units of analysis not specified in the original terms of reference of a study (e.g. from animals to humans, from a tested drug to an untested drug, etc.).

2. Conclusions derived from a single trial (a) when the population from which the sample was drawn has not been fully described, (b) which are generalized to all possible units, and (c) in which an insufficient number of cases has been used (e.g. reporting that a drug or therapy is effective for all patients with a given disease where the population has been unspecified and the results have been obtained from only 10 to 20 cases).

3. Conclusions pertaining to cause and effect (a) where only variation in the relationship of the variables has been shown and (b) where no control group has been used (e.g. concluding definitively about the effect of a particular event on the structure of human personality from a study of 12 families. Families not undergoing the event were not considered.).

The difficulties listed above are additive, not mutually exclusive categories. In 41.5% of the articles analyzed, *one or more* of the difficulties was noted. Since conclusions in research may be stepping-stones for action, this finding suggests for the studies considered that their results and conclusions should be carefully re-examined for possible alternative interpretations.

SUMMARY

To provide medical students with a basis for assessing the methodology of research studies, 103 articles using group data were reviewed. The analysis focused on (1) the definition of terms, (2) the selection of a population or sample, (3) the use of controls, (4) types of statistical analysis, and (5) the derivation of conclusions. For the articles under review, this assess-

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ment revealed the need for greater precision in the design of many studies using group data and for caution in the interpretation of results.

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REVIEW ARTICLE

MYOTONIA DYSTROPHIA: A REVIEW OF 17 CASES

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MYOTONIA dystrophia is an heredo-familial degeneration characterized by myotonia, selective atrophy of the muscles, and dystrophic signs in other tissues including baldness, cataracts, testicular atrophy and dysfunction of the endocrine glands. This report, listed in Tables I and II, details observations on 17 patients with this condition, encountered at Sunnybrook Hospital, Toronto, between 1948 and 1960.

HISTORY

Since Erb's monograph in 1886, describing atypical forms of Thomsen's disease in which the association of myotonia with atrophy of the muscles was recognized, our understanding of this condition has burgeoned from its original narrow concept to that of a multisystem process involving various tissues and organs. Deleage, in 1890, was the first to describe this curious combination of symptoms as a distinct entity, while Rossolimo, a few years later, offered the nomenclature of myotonia atrophia for those cases in which atrophy supervened. In 1909, Batten and Gibb,[5] and Steinert,[41] simultaneously but independently, stated that the myotonia was limited in its distribution and that the atrophy showed a characteristic pattern with involvement of the facies, the sternocleidomastoid muscles, the muscles of the forearm, the extensors of the legs, and the dorsiflexors of the feet. Batton gave priority to the atrophy, stating that the myotonia was a secondary symptom. Steinert stressed the myotonia but also drew attention to the importance of the widespread dystrophic process which included testicular atrophy, baldness and acrocyanosis. Adie and Greenfield,[2] in 1911, showed that cataracts were an integral part of the syndrome when he described a family of 13 brothers and sisters of whom five suffered from myotonia dystrophia; two of the affected five had cataracts, while two others, otherwise unaffected, also suffered from cataracts. Curschmann[13] emphasized the extramuscular manifestations and coined the name myotonia dystrophia. However, the etiology remained obscure until Fleischer,[17] in 1918, showed that myotonia dystrophia was an heredo-familial degenerative disease exhibiting anticipatory signs through several generations before it developed entirely in one generation. He traced the disease through six generations and demonstrated how it burst forth in a number of families at the same distance from the common ancestor.

ONSET

The onset of dystrophia myotonia occurs commonly in the second or third decade, with weakness as the prevailing complaint. However, the age of onset varies markedly with the generation affected, since in antecedent generations the disease begins at a later age and rarely progresses to a point where the diagnosis is made before death. When the diagnosis is made in an affected child, it is often in retrospect that the features of baldness and senile cataracts are recognized as strongly suggestive evidence that the parent also suffered from the disease. Conversely, the offspring of those affected in the third and fourth generations may be expected to show the disease in the second or even first decade of life. The insidious nature of the disease and the slowness with which it progresses allows a considerable lapse of time between the commencement of symptoms and the request for relief because of disablement. Patients often compensate and accept early symptoms, so that initial hospital admission may be for treatment and in-

TABLE I.

Case No.	Age of onset years	Marital status	Children	Presenting symptoms	Family history	Relation	Symptomatic myotonia	Percussion myotonia	Muscular Atrophy					Deep reflexes	Gait
									Facies	Sternocleido mastoid muscles	Forearm muscles	Ext. muscles of leg	Dorsiflexors of foot		
1	33	S	—	Weakness	Early baldness	Father, grandfather	Present	Present	Myopathic	++++	+++	++++	++++	Feeble	Normal
2	17	S	—	Weakness	Myotonia dystrophia	Cousin	Present	Absent	Myopathic	+++	+++	++	++	Feeble	Steppage
3	24	M	0	Weakness	—	—	Present	Present	Myopathic	+++	+++	+	+	Normal	Normal
4	23	S	—	Myotonia	Cataracts	Brother, sister	Present	Present	Myopathic	++	++	++	++++	Absent	Steppage
5	25	S	—	Weakness	Early baldness	Father, grand father	Present	Present	Myopathic	++	+	+	+++	Absent	Steppage
6	10	Separated	—	Myotonia	Myotonia dystrophia	Father	Present	Present	Myopathic	+++	++	++	++++	Feeble	Steppage
7	46	M	1	Headaches	Myotonia	Daughter	Present	Present	Myopathic	++	+	+	—	Normal	Normal
8	25	S	—	Weakness, poor vision	Myotonia dystrophia	Uncle	Present	Present	Myopathic	+++	++	++	++	Normal	Normal
9	32	M	1	Weakness, myotonia	—	—	Present	Absent	Myopathic	++	+++	+	+++	Absent	Steppage
10	43	S	—	Poor vision	Cataracts	Mother	Present	Present	Myopathic	+++	++	—	++	Normal	Normal
11	49	M	0	Poor vision, weakness	—	—	Present	Present	Myopathic	+++	+++	+	++	Absent	Normal
12	34	S	—	Broncho-pneumonia	Cataracts	Mother, uncle	Present	Present	Myopathic	++++	+++	+	+++	Absent	Steppage
13	33	M	3	Poor vision	—	—	Present	Present	Myopathic	++	+++	+	+	Feeble	Normal
14	37	M	4	Poor vision	—	—	Present	Absent	Myopathic	+++	++	+	++	Feeble	Normal
15	19	M	3	Weakness, poor vision	Cataracts	Father	Present	Present	Myopathic	++++	+	—	+++	Feeble	Steppage
16	27	S	—	Poor vision	Cataracts	Father	Present	Present	—	++	—	—	—	Normal	Normal
17	?67	M	1	Poor vision	Myotonia dystrophia	Son	Present	Absent	—	+	—	—	—	Normal	Normal

++++ — Severe.
+++ — Handicapping.
++ — Symptom-producing but not handicapping.
+ — Demonstrable on objective testing.

vestigation of entirely unrelated conditions. In our group, one patient came to hospital with bronchopneumonia while the chief complaint of another on admission was headaches.

The majority of our patients (10) were in the second to fourth decade. One patient dated his symptoms back to the age of ten years (Case 6); another, a man of 67 (Case 17) with bilateral senile cataracts, was not diagnosed until his son presented with the full pattern of the disease.

The onset of the initial symptom is elusive to define. However, it is believed that the myotonia, whether recognized or not by the patient, usually precedes the atrophy by several years.[1, 2] The fact that only three of our 17 patients presented with myotonia as their chief complaint indicates the significance of this symptom. Five patients reported weakness, five complained of loss of vision, and three had weakness and loss of vision: yet all had symptomatic myotonia with objective testing. Thus it is apparent that the myotonia, which is a constant and cardinal aspect of this disease, is of secondary importance to the patient. Distress usually results from debilitating atrophy or loss of vision.

Both sexes are affected, with a slight preponderance in males.

MYOTONIA

Myotonia is defined as the failure of muscles to relax properly after a forceful contraction. The delay in relaxation may persist 30 seconds or longer after the stimulus producing it has ceased. The myotonia of myotonia dystrophia is not widespread as it is in Thomsen's disease, and is present generally in the hands, tongue and facial muscles. This is usually expressed as a difficulty in chewing, swallowing, or taking or relaxing a hand grip. If present in the lower limbs, it is indicated by stiffness of the knees on squatting, or fixation of the legs when a sudden movement is attempted. It is usually painless but occasionally can cause muscle cramps.

Gentle movements do not cause myotonia, so that blinking and movements of facial expression may be performed freely. It is the sudden voluntary movement put forth with vigour that produces the typical myotonic response. Thus there is a direct relationship between the force of contraction, up to a certain limit, and the degree of active myotonia elicited. This response is often intensified by emotional excitement and cold weather. Usually the muscular stiffness which results from myotonia

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is temporarily relieved by repeated voluntary contractions, but there are occasional cases in which it is accentuated by exercise (myotonia paradoxica).

Ravin,[36] in 1940, carried out ergographic studies on the movements of the thumb in patients with myotonia dystrophia. He concluded that myotonia is actually an abnormal persistence of the state of contraction, since relaxation is, in effect, a passive process depending on the subsidence of that state of contraction. Also, he found that the myotonia set in only when the muscle contracted and not during the maintenance of contraction. Thus he established that the production of myotonia depended on the occurrence of those changes in muscle, associated with the actual contraction or shortening of the muscle, rather than on the nature of the stimulus producing the contraction.

Percussion myotonia, elicited most constantly in the tongue, face, and the muscles of the thenar and hypothenar eminences, is best demonstrated in muscles which show little or no atrophy, as the myotonia may disappear when extensive atrophy develops. Paradoxically, mechanical myotonia may be demonstrated in muscles not displaying active myotonia and *vice versa*.

ATROPHY

Selective atrophy is found in the muscles of the face, sternomastoids, forearm, vasti and dorsiflexors of the foot, in a symmetrical fashion. The geographical involvement of these muscle groups is generally constant, but as the condition becomes moderately advanced, other groups are in turn affected. Variations from this pattern in terms of early involvement of the shoulder and pelvic girdle have been described,[27] but such cases are in the minority.

Atrophy of the muscles of the face produces the gloomy mien of the characteristic myopathic facies (Fig. 1). The face is long, wan and bony owing to wasting of the temporals and muscles of expression. Facial expression is minimal; the forehead is smooth and unlined, the mouth is pouted, and the lips sag with involvement of the orbicularis oris. Weakness of the levator palpebrae superioris and orbicularis oculi results in ptosis and infrequent blinking. Atrophy and weakness of the muscles of the pharynx result in a monotous, inarticular manner of speech with a distinctive nasal twang.

The sternocleidomastoids are affected almost invariably. Patients may be unable to lift their heads from the supine position or to perform sharp, swift rotatory movements of the neck. In the presence of severe atrophy only a few shreds of this muscle may be present, giving the thin neck with an exaggerated forward curvature a swan-like appearance.

The diaphragm may become involved either unilaterally or bilaterally, as manifested by elevation of one or both hemidiaphragms.[11]

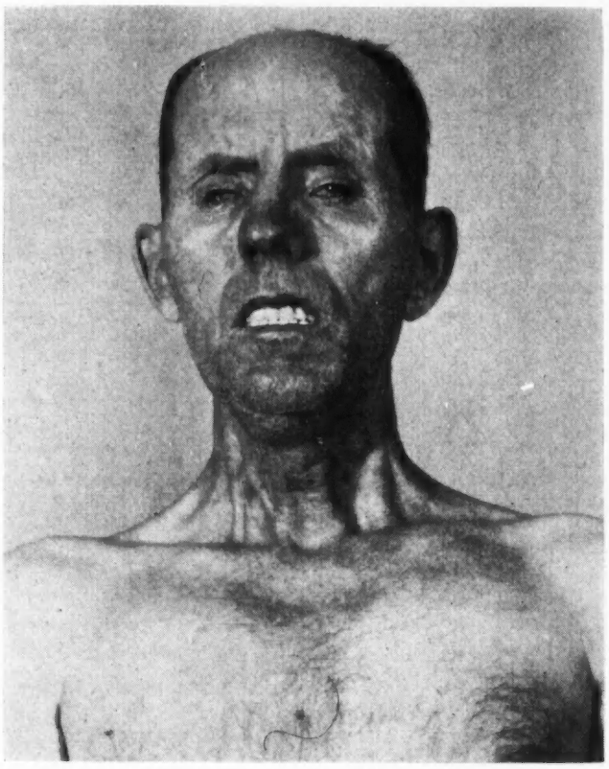

Fig. 1.—This illustrates the typical myopathic facies with atrophy of the sternocleidomastoids; blepharo-conjunctivitis is also present.

In the limbs there is greater variability in the spread of involvement. The extensor muscles of the forearm appear to be affected earlier and more severely than the flexors. However, wasting and weakness are commonly observed in the brachioradialis and small muscles of the hand, especially the muscles of the thenar and hypothenar eminences. The interosseous muscles usually atrophy later.

Atrophy of the vastus muscles and dorsiflexors of the feet results in a broad-based, steppage gait. The forefeet are lifted poorly in walking, so that a high type of march is necessary for clearance. Foot drop is common. Several of our patients presented because of a threatening tendency to fall owing to weakness of the dorsiflexors of the feet.

The deep reflexes are commonly feeble or absent and this is most obvious in the severely atrophic muscle groups. However, absent or depressed reflexes may be found in the muscles which are not atrophic. The cutaneous reflexes, on the other hand, are generally normal.

Hypertrophy, which is invariably a feature of Thomsen's disease, is not prominent in myotonia dystrophia. In Thomsen's disease, the fulsome large muscles may give patients a Herculean appearance whereas in myotonia dystrophia the patients are characteristically asthenic. Maas and Paterson[31] and Caughey[8] have reported cases in which apparent hypertrophy of the muscles was evident in isolated muscle groups in patients with myotonia dystrophia. Greenfield *et al.*[2] deny that hypertrophy occurs in this disease and feel that

the striking contrast in the size of the muscles free from atrophy, beside those which have wasted, creates an illusion of hypertrophy. In this group of patients, true hypertrophy or pseudohypertrophy was not present.

The progress of the atrophy is variable. The wasting and accompanying weakness may become stationary, so that the patient is able to carry on with his normal routine. More frequently it is progressively severe with general deterioration, loss of weight, and emaciation. With involvement of the muscles of the trunk, the patient may be reduced to a bed-ridden invalid.

HEREDITY

Myotonia dystrophia is a familial disease transmitted by a modified autosomal dominant gene. The gene may be transmitted through several generations with very few or slight signs of the disease apparent. In this series, only one patient (Case 6) with the full-blown disease had a parent who was similarly affected. For the rest, the presence of senile cataracts, early baldness, or mild myotonia were the sole indications that their parents or grandparents possessed the defective gene. An extensive investigation into pedigrees was not carried out; the absence of a familial history in five of our patients was not considered to be significant. Geneological surveys often must be carried back several generations in order to establish the familial character of the disease.

The fact that most parents of our affected patients were healthy precludes transmission by a simple dominant gene. Thus a modified dominant gene has been postulated[37] to explain the apparent dislocation of signs found in antecedent generations. There is little evidence that the nature of transmission is by a recessive gene. Maas[27] and Kolb, Harvey and Whitehill[25] have reported the occurrence of myotonia dystrophia in half-brothers and half-sisters. Since the incidence of myotonia dystrophia has been estimated at 1 in 100,000, it would be labouring the mathematics of chance to assume that this was the product of a recessive trait. Moreover, Ravin and Waring[37] have found that consanguineous marriages were not common among the parents of their patients.

In successive generations the disease sets in at earlier ages until in one generation the complete syndrome of myotonia dystrophia appears; then the disease is transmitted as a simple dominant from parent to offspring. In the links of the descending family tree the disease not only has an earlier onset but is more severe in succeeding generations. The latent carriage of a defective gene coupled with the progressive involvement of that defect has been referred to as the phenomenon of anticipation and potentiation. Singularly the term progressive inheritance is employed.

Maas has reported that the disease is more severe and has an earlier onset in the younger siblings of a sibship. Thomasen,[42] on the other hand, has not found a striking degree of "fraternal anticipation and potentiation" in his case studies. He points out that the degree of the disease, as might be expected, is rather more pronounced in those siblings who have had it for the longest periods.

Eventually dystrophic features become evident before the affected individual reaches full maturity and the disease ceases to appear in that family. This was evident in our group as eight patients were single, two were married with no offspring, and one was separated but childless. Two married patients had only one child while the other three patients, not severely affected, had as many as three and four children each.

Maas and Paterson[27-31] have raised strong objections to the sequestration of myotonia dystrophia as a disease entity. They contend that myotonia congenita, the paramyotonias and myotonia dystrophia should be grouped together, as one is a mere variant of the others. They cite cases of a hybrid nature in which the characteristics displayed could not be defined clearly as belonging to one disease or the other. This argument if held lends greater confusion to the mechanism of heredity, as myotonia congenita is transmitted as a pure Mendelian dominant.

However, most authors[42, 47] believe that myotonic dystrophia should be regarded as a separate entity distinct from myotonia congenita and the paramyotonias. Moreover, it is felt that transmission in this condition is via a single factor dominance, modified by the occurrence of progressive inheritance. The main criticism of this hypothesis is that observations have been made on selected material of patients with myotonia dystrophia because in the foregoing generations only the least affected are able to have children.

PATHOLOGY

The histopathological findings encountered in two autopsies and four muscle biopsies were centred about the muscles, testes, heart and endocrine glands.

In the muscles the histological appearance and the degree of change encountered were in direct relationship to the severity of wasting and had no bearing on the degree of myotonia. In our specimens there was striking variation in the size of the individual fibres, as large and very small fibres were scattered in a haphazard arrangement throughout the one specimen. There was not a clear, definitive arrangement into stages, suggesting a complete muscular change from one phase to another. Various aspects of muscular degeneration were evident in any one section.

In the early stages there is proliferation of sarcolemma nuclei giving rise to dense chains of nuclei along the borders of muscle fibres and even between the muscle fibres. As degeneration sets in, the

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sarcolemmal nuclei pass to the centre of the muscle fibres and arrange themselves in lines both inside it and along the surface (Figs. 2, 3 and 4). Besides the thick peripheral layer of sarcoplasm enveloping the muscle fibre, there is interstitial connective tissue proliferation and fatty replacement between the fibres. In the final stages of atrophy shreds of extremely wasted muscle fibres are seen embedded in the dense connective tissue containing fat.

The presence of central chains of nuclei in the muscle fibre and the sarcoplasmic thickenings are not specific for myotonia dystrophia, as they are seen in progressive muscular dystrophy and myotonia congenita. Connective tissue proliferation merely indicates the end stages of degenerating muscle tissue. Sarcoplasmic masses either centrally or eccentrically placed in the muscle fibre constitute the only change found in biopsy specimens[19] that can be regarded as pathognomonic for myotonia dystrophia. Frequent ringed fibres within the muscle fibre itself are highly suggestive of myotonic muscle.

Most authors[1, 20, 49] concur that the central nervous system, spinal cord, sympathetic chains, peripheral nerves and neuromuscular functions are not affected in this condition.

In both of our autopsied cases the testes were grossly atrophic. On the cut section there was considerable atrophy and sclerosis of many seminiferous tubules, some of the tubules still showing spermatogenesis. The interstitial cells of Leydig were normal or decreased in number.

The histological changes in the heart are described elsewhere in this article.

Black and Ravin[6] reported that in four of their five cases the adrenal glands showed a degree of cortical atrophy, particularly affecting the zone fasciculata, with island grouping of cells containing lipoid material, Keschner and Davison[24] also described atrophy of the fascicular layer of the adrenals with a loss of cells. In one of our cases the adrenals were normal, while the other showed diffuse cortical hyperplasia.

In our sections, the pituitary glands were unremarkable. However, isolated findings recorded in the literature include small cysts in the pars intermedia,[2] atrophy of the anterior lobe with a relative increase in basophilic cells,[7] and hyperplasia of acidophilic cells.[24]

In one of our autopsied cases the thyroid gland weighed over 40 g. and displayed an encapsulated focus of nodular hyperplasia. In the other case the thyroid weighed 10 g. and showed some diffuse non-specific hyperplasia. Although thyroid atrophy has been described in this disease,[42] there was no definite correlation between the histological picture of the thyroid gland and the basal metabolic rate, in these patients.

The reported changes in the endocrine glands, both clinically and at autopsy, are frequent enough to warrant attention. However, the lack of constant findings in any particular gland or glands prohibits definition of the site and nature of the vague disorder of the endocrines. Only in the gonads have

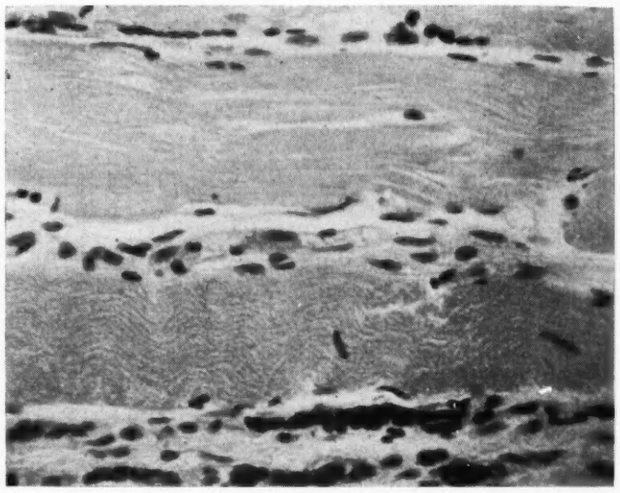

Fig. 2.—Section of muscle. Thickening of the sarcolemma sheath is seen with chains of dark-staining nuclei. A moderate amount of connective tissue proliferation is present. (H. & E.)

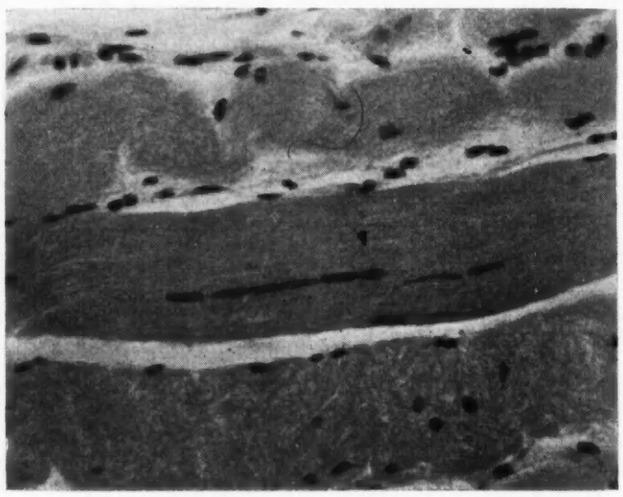

Fig. 3.—Section of muscle. Centrally placed muscle nuclei are forming links. Muscle fibre is not atrophic. (H. & E.)

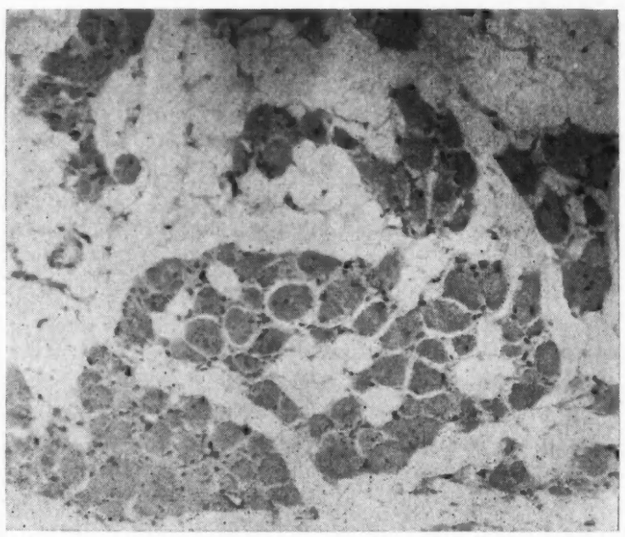

Fig. 4.—Cross-section of muscle. Wide variability of muscle fibre size is seen. Many central muscle nuclei are present. Note abundant fatty infiltration. (H. & E.)

TABLE II.

Case No.	Cataracts	Ocular complaints on admission	Other changes	Blood pressure (mm.Hg)	Pulse	P-R interval (sec.)	QRS (sec.)		Early baldness	Testicular atrophy	Response to quinine	Cause of death
1	Polychromatic	—	Macular degeneration	100/70	74	0.22	0.12	Left bundle branch block and left ventricular hypertrophy	Present	Present	Poor	
2	No slit lamp examination	—	Macular degeneration	135/75	72	—	—	—	Present	Present	Good	
3	Polychromatic	—	Blepharo-conjunctivitis	138/70	72	—	—	—	Present	Present	Discont.	
4	Polychromatic	—	—	112/89	100	—	0.08	Atrial fibrillation	Present	Present	Fair	Pneumonia and pulmonary embolus
5	No slit lamp examination	—	—	115/68	75	0.16	0.08	—	Present	Absent	—	
6	Mature	—	—	130/80	80	—	—	—	Present	Present	Discont.	
7	None	—	—	130/85	72	0.24	0.08	—	Present	Present	Poor	
8	Polychromatic	Present	Macular degeneration	110/78	74	0.16	0.06	—	Present	Present	—	
9	Polychromatic	—	Macular degeneration	90/50	60	0.24	0.010	—	Present	Minimal	None	Broncho-pneumonia, empyema
10	Mature	Present	Blepharo-conjunctivitis	90/70	64	0.20	0.08	Atheroma post mortem	Present	Absent	—	Hepatic failure
11	Mature	Present	—	95/65	66	0.32	0.20	Left bundle branch block and left ventricular hypertrophy	Absent	Present	—	Myocardial infarction
12	Polychromatic	—	—	124/84	76	0.18	0.06	—	Present	Present	Fair	
13	Mature	Present	Blepharo-conjunctivitis	90/55	84	0.16	0.08	L. axis deviation	Present	Present	—	
14	Polychromatic	Present	Bilateral iridocyclitis, blepharo-conjunctivitis	100/65	68	—	—		Present	Present	Fair	
15	Polychromatic	Present	Bilateral ectropia	100/65	48	0.22	0.12	—	Present	Absent	Good	
16	Polychromatic	Present	Bilateral iridocylitis	108/70	60	0.16	0.08	—	Present	Present	Good	
17	Mature	Present	Blepharo-conjunctivitis	90/60	68	0.20	0.08	L. axis deviation	Absent	Absent	—	

the clinical-pathological impressions offered a comprehensive picture which one can readily observe in myotonia dystrophia.

OCULAR MANIFESTATIONS

Hoffman, in 1912, estimated that 10% of patients with myotonia dystrophia had cataracts. Ravin and Waring,[37] in 1940, found that 12 of their 13 patients had cataracts, while Allen and Barer[3] observed lenticular changes in all 21 patients subjected to slit lamp examination. In this review, 14 patients were found to have cataracts, nine of these demonstrating polychromasia and five possessing a senile type either in an incipient or a mature stage. Two of the three patients in whom a cataract could not be detected did not receive a slit lamp examination. Those affected with polychromatic cataracts often did not have visual disturbances. Loss of vision generally does not occur until widespread lenticular opacification takes place.

Senile cataracts may be the only sign in patients possessing the gene of myotonia dystrophia. The fully developed disease may appear in their children. In such cases the cataract usually appears at an earlier age and is pre-senile in character. This was shown by Fleischer,[17] who found senile cataracts occurring in an affected family at the ages of 37, 38, 52 and 65 years, and pre-senile cataracts in the following dystrophic generation at the ages of 27, 30, 31 and 40 years.

On slit lamp examination the pathognomonic features are the presence of dustlike and punctate opacities intermingled with larger angular flakes, producing an iridescent display of scintillating colours, mainly red, green and blue (Fig. 5). The earliest changes occur at the posterior cortical region just under the capsule. Frequently a stellate group of opacities accumulate at the posterior pole which represents progressive opacification of the lens fibres along the suture lines. At this stage, the condition may remain stationary for several years with minimal or no loss of vision. Anterior subcapsular deposits were seen generally when the posterior deposits were already present. At a later date, and this may occur 10 or 20 years later, deep cortical opacities and lamellar separations form with the development of a soft cataract with a small nucleus. The senile cataract is not distinctive and resembles the ordinary cataract often seen with ageing.

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A chronic blepharo-conjunctivitis was seen in five cases of our group. Waring, Ravin and Walker[47] found that nine of their 13 cases had chronic blepharo-conjunctivitis.

Macular and paramacular degeneration, viewed as a greyish-white stippling in these areas, was discovered in four cases; one patient was in the third decade, two were in the fourth decade, and one was in the fifth. The only reference to this change found in the literature was that reported in 1947 by Verry,[46] who observed macular degeneration in a young patient with myotonia dystrophia. There is a condition of heredo-macular degeneration characterized by bilateral degenerative changes at the macular area without degenerative changes in the central nervous system. Whether myotonia dystrophia fits into the collected group of diseases manifesting this change awaits further confirmation and study.

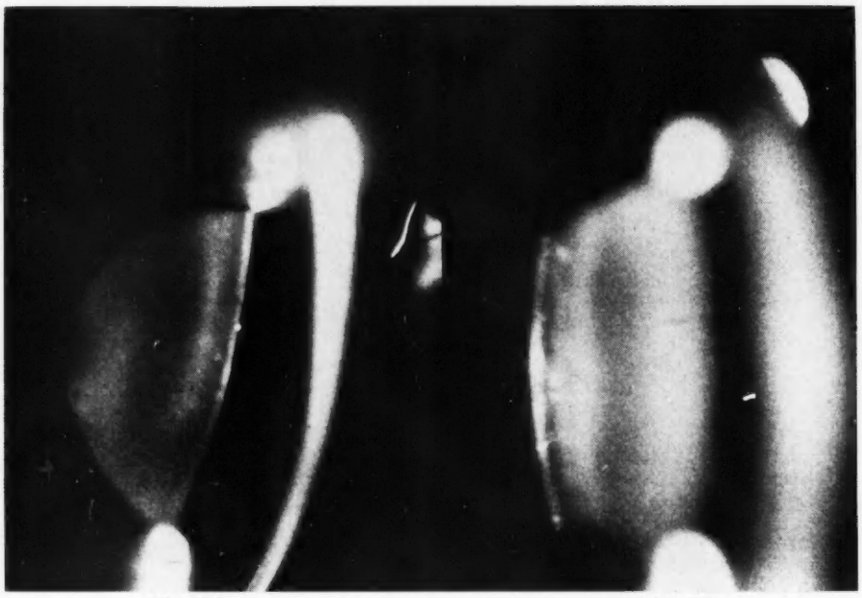

Fig. 5A Fig. 5B

Fig. 5.—Slit lamp photograph of the lens (Cases 8 and 12). Note the anterior (A) and posterior (B) subcapsular deposits, viewed as red and green crystals. Also note the opacification within the lens, more marked in (B).

Verbiest,[46] in 1937, described another obscure ocular manifestation which has not as yet received recognition as a feature of this condition. He reported a patient with myotonia dystrophia who exhibited myotonic convergent movements of the eyes which were accompanied by narrowing of the pupils. Lateral conjugate movements of the eyes were carried out normally, but when the eyes converged, they could not diverge immediately for distant vision. This interesting phenomenon was not noted in our group.

Two patients in this series had bilateral iridocyclitis. The following is a report of the findings in one of these patients: This 28-year-old single man (Case 16) came to the ophthalmology service because of some intermittent blurring of vision associated with photophobia and excessive lacrimation. He also noticed particles floating in front of the field of vision of each eye and halo formation about lights. His father (Case 17) had cataracts at the age of 47. On examination, he was an obese man with a receding hairline. His height was 72 inches and his span 74 inches. The vitreous was cloudy bilaterally. There were some ruby-red and turquoise iridescent crystals in a single layer anterior to the posterior capsule. The cornea was clear except for pigment clumping on the endothelial surface of each eye. The blood pressure was 118/80 mm. Hg and the pulse rate 68 per minute. There was active myotonia and slight wasting of the sternocleidomastoids. The testes were small and soft.

The various known causes of iridocyclitis were searched for and ruled out as far as possible by various laboratory tests. Since an etiological agent was not revealed, the occurrence of iridocyclitis in these two cases would seem to be idiopathic and coincidental, or related to the dystrophic process by some means not fully understood as yet.

It is of clinical significance that eight of our 17 cases presented with some disturbance of ocular function. Allen and Barer[3] found that seven of their patients, or one-third, entered hospital because of loss of vision, while two others were seen because of chronic blepharoconjunctivitis.

Diplopia or paralysis of ocular rotation was not observed. Bilateral ptosis due to atrophy of the orbicularis oculi and levator palpebrae superioris was a frequent finding. One patient had an ectropion.

The ocular manifestations of this disease are numerous, with cataracts the most constant finding and loss of vision a prominent presenting symptom.

CARDIOVASCULAR SYSTEM

The disturbances in the cardiovascular system are indicated by changes in blood pressure, pulse and the electrocardiogram. The disturbances are mild and do not offer any incapacity to the patient. Indeed, none of the patients in this group complained of chest pain, palpitations or respiratory distress at a time when electrocardiographic changes were manifest. Six patients complained of coldness of the hands and feet, irrespective of temperature, with mottled cyanosis in cold weather. One patient with non-specific electrocardiographic findings died of myocardial infarction. However, at autopsy atheromatous plaques were found in both coronary vessels. In view of the atheromatous changes found, it is unlikely that the episode of myocardial infarction was related to any cardiac manifestations of myotonia dystrophia.

The blood pressure is often low, and bradycardia with a soft pulse is usual.[14, 40] A drop in the

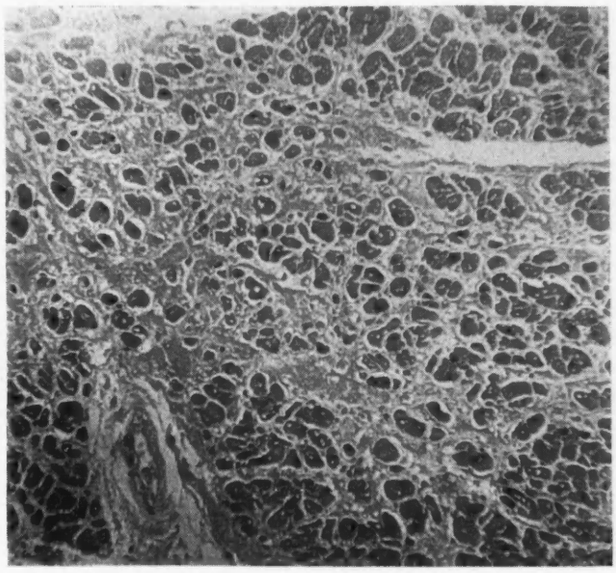

Fig. 6.—Cross-section of myocardium (Case 9). Patchy diffuse fibrosis with replacement and loss of muscle fibres in the myocardium. Age of patient at death was 45.

systolic pressure was most commonly observed. In four cases the systolic pressure was 90 mm. Hg, while in four others the systolic pressures were 100 mm. Hg or less. In none of our cases was the blood pressure raised. The patients were 25 years of age or older when these recordings were noted. The pulse rate was below 70 per minute in seven cases. None of these patients complained of faintness, giddiness or syncopal attacks.

The chief abnormality in the 13 available electrocardiographs was a disturbance of conduction. The PR interval was 0.2 second or greater in seven cases. A prolonged intraventricular conduction time, in which the QRS was 0.12 second, was found in three cases. Two patients showed left bundle branch block. One patient with atrial fibrillation had physical findings of widespread atherosclerosis. Of the patients demonstrating these changes of conduction only three were taking quinine. Thus, electrocardiographic changes in this series cannot be attributed to quinine, since five of our patients were not given this drug. Also, quinine withdrawal in two cases did not correct the previously noted electrocardiographic defects. Changes noted by others[14, 15] in the electrocardiographs include low voltage P-waves and left axis deviation. In this group, low voltage P-waves were found in four cases and left axis deviation in only two.

The radiological examinations of the chest were unremarkable except in two cases in which mild left ventricular hypertrophy was noted.

There has been no constant correlation between the clinically observed findings in the heart and those discovered at postmortem examination. Black and Ravin[6] found no abnormality in the hearts of five patients who were examined postmortem. Wohlfart's[49] findings were similar. However, in 1954, Fisch and Evans[16] reported one case of diffuse myocardial fibrosis with separation of the muscle fibres by fairly dense connective tissue. The coronary vessels were normal. Keschner and Davison[24] reported displacement of muscle fibres of the heart with fat cells. In one of our autopsied cases (Case 16) patchy scarring of the myocardium was present but the coronary arteries showed advanced atherosclerotic changes. In the other case (Case 9) the coronary vessels were normal but the myocardium displayed diffuse irregular patches of fibrosis extending between the muscle fibres. The intervening muscle fibres appeared normal (Fig. 6). In this case the electrocardiogram showed a P-R interval of 0.24 second and a QRS of 0.10 second (Fig. 7). Certainly it is tempting to relate the conduction defects clinically observed with dystrophic changes in the heart seen at autopsy. However, until further evidence is forthcoming, the only conclusions that can be drawn are: (1) Degeneration of the muscle fibres with fatty or fibrous tissue replacement is not a constant feature of this disease. (2) The changes in the microscopic sections in skeletal muscle do not parallel those changes which have been described in cardiac muscle.

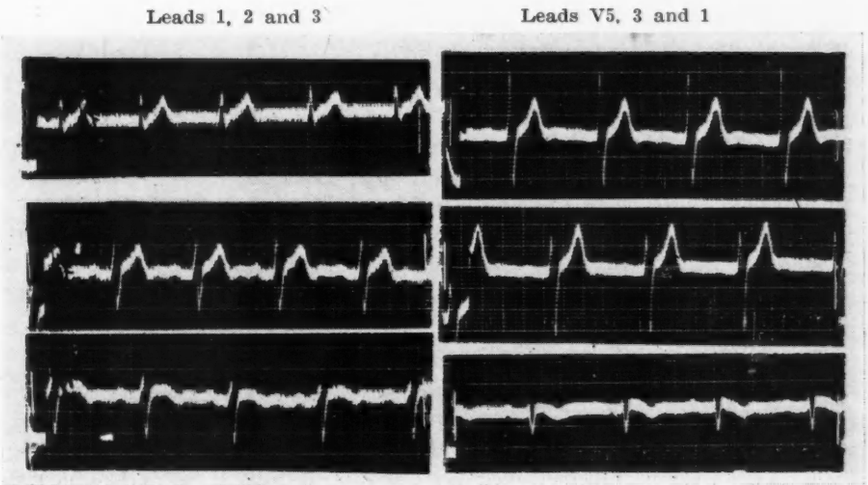

Fig. 7.—Electrocardiograph (Case 9), demonstrating mild conduction defects. P-R interval is 0.24 sec.; QRS, 0.10 sec. Coronaries were normal. Age of patient was 36. Autopsy specimen of myocardium in this case is illustrated in Fig. 6.

ENDOCRINE CHANGES

The endocrine changes associated with myotonia dystrophia are marked by clinical signs of hypogonadism. Dysfunction of the adrenals and thyroid is not clinically apparent but is suggested by abnormal laboratory findings.

Testicular atrophy is a common feature of this disease and was present in 13 patients in this series.

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The onset of gonadal hypofunction occurs after puberty, as is evident from the normal skeletal proportions, voice pitch, development of secondary sex characteristics and the normal radiological appearances of the long bones. Moreover, the nuclear sex chromatin pattern is quite appropriate to the phenotype sex. This was shown by Marshall and Thomas,[33] who studied buccal smears on 19 cases. Symptoms commence in the middle twenties. In the male they consist of loss of libido, impotence and sterility; in the female, hypogonadism is manifested by menstrual irregularities and infertility.

Premature baldness, noted in 15 patients of our group, is almost a constant sign. The hair on the face, axilla and pubis is generally of normal texture and appropriate to the sex of the patient. In a few cases the growth of hair in these areas was considered scant.

Although enlargement of the thyroid[47] is frequently reported, overt signs of myxedema are not evident. The basal metabolic rate is invariably low, but the serum cholesterol values are normal and substitution therapy has no beneficial effect. Myxedema associated with myotonia itself, Hoffman's syndrome, has been described.[42] In these cases, myxedema and myotonia disappear after administration of thyroid preparations.

There is no evidence to indicate involvement of the parathyroids. Serum calcium and phosphorus determinations in our patients were normal. Moreover, the cataracts of tetany are quite different from those found in myotonia dystrophia.

Adrenal function studies were not carried out extensively in this group. However, Caughey and Brown[9] reported that in nine cases the 24-hour urinary excretion of 17-ketosteroids ranged between 1.0 mg. and 5.5 mg., with an average excretion of 2.8 mg. Benda and Bixby[7] reported five cases in which the daily output ranged between 2.8 mg. and 8.0 mg., with an average of 5.5 mg. Other workers[12] also have confirmed that the level of resting urinary 17-ketosteroids is low in this condition.

The fatigue, weakness, bradycardia and relative hypotension may be construed as evidence of hypofunction of the adrenal cortex. However, electrolyte studies in this group have shown the serum potassium, sodium and chlorides to be normal. Moreover, steroid replacement has yielded equivocal results in terms of improving muscle strength or myotonia.[4, 39]

Lesions of the hypothalamus and hypophysis have been viewed speculatively as the primary cause of gonadal dystrophy, asthesnia, somnolence and the minor disorders of the thyroid and adrenals in this condition. But the degenerative cellular changes described in the pituitary from postmortem examination have lacked repeated confirmation and thus fail to be convincing. Moreover, Caughey and Brown[9] found a follicle-stimulating hormone (FSH) level of 96 mouse units in three of nine patients and noted that the level of this hormone was never abnormally low. This result would weigh against the existence of primary pituitary failure in this disease.

The abnormal creatinuria and decreased creatinine output found in myotonia dystrophia is merely a reflection of the degree of muscular wasting and is seen in progressive muscular dystrophies, hyperthyroidism, poliomyelitis and other disorders associated with progressive atrophy of muscles.

RADIOGRAPHIC CHANGES

Caughey,[10] in 1950, presented a comprehensive description of the radiographic changes in the skull encountered in myotonia dystrophia. The prominent features in his 13 cases were a small sella turcica, thickening of the calvarium, hyperostosis interna frontalis and parietalis, and enlargement of the sinuses. Less conspicuous and less frequent manifestations were pneumatization of the dorsum sella, elongation of the mandible, prominent venous lacunae, increased bony density and calcification within the sella turcica. In the 10 cases in this group in which skull radiographs were taken, the findings were comparable to those described by Caughey. The films were reviewed by comparing and contrasting them with 10 normal skull films, selected at random. The ages of patients in the dystrophic group, when these films were taken ranged from 26 to 49 years; those in the control group were from 22 to 66, the majority being in the third and fourth decade. In six cases the teeth were absent and the degree of elongation of the mandible could not be estimated. If the lower teeth approximated the uppers or extended beyond them, the mandible was considered to be slightly or markedly elongated.

	Control	*Myotonia dystrophia*
1. Enlargement of sinuses	3	7
2. Thickening of bones of calvarium	1	8
3. Small sella turcica	3	8
4. Hyperostosis frontalis	1	3
5. Elongation of the mandible	3 of 5	5 of 9
6. Prominent venous markings	2	2
7. Pneumatization of the dorsum sellae	2	3

As this series is too small to be considered statistically valid, the findings reported in the skull films must be regarded as indicative of a trend rather than as proved facts. None of the radiographic signs appear to be specific, for they were observed amongst our controls, and indeed are seen in other conditions, e.g. dense cranial vault in Paget's disease. The significant findings suggested by this trend are enlargement of the sinuses, thickened bones of the calvarium and small sella turcica (Fig. 8). The presence of hyperostosis frontalis and elongation of the mandible observed by Caughey[10] were not prominent among the patients investigated in this study. In terms of clinical application the radiological changes in the skull, once established, may offer further diagnostic evidence in support of the diagnosis of myotonia dystrophia.

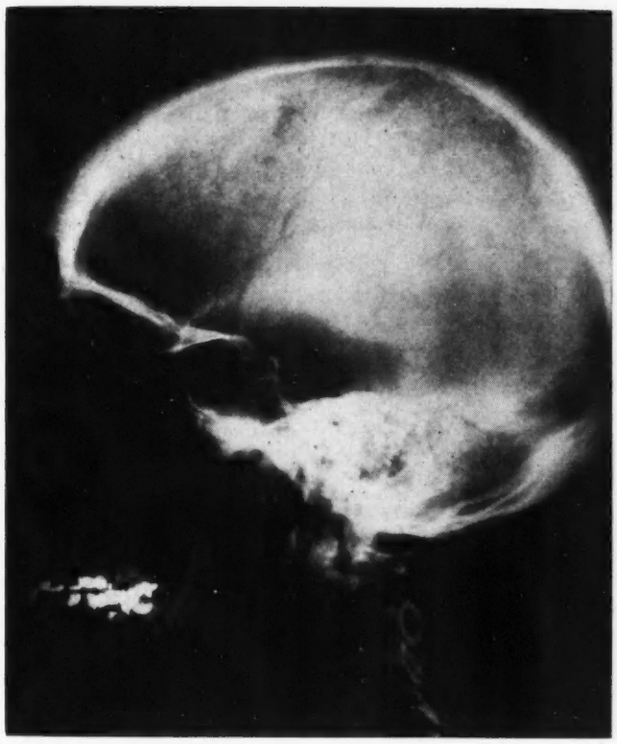

Fig. 8.—Radiograph of skull illustrating the dense cranial vault, small sella, and enlargement of the sinuses.

MENTAL CHANGES

Mental retardation may accompany the other dystrophic features of this disease. Besides low intelligence, Maas and Paterson[25] described a constant temperament in their patients, characterized by inappropriate cheerfulness, mild grandiosity and relative lack of drive. They found the most severe mental changes in patients with advanced muscular wasting. Fleischer,[17] in his family studies, noted a steady decline of the family fortunes from positions of comparative affluence to states of poverty. Adie and Greenfield[2] noted that the intellectual attainments were not high, but also observed that this was not surprising, since the cases studied belonged to the lower socio-economic classes.

Our group suffered from the same bias. It was composed of male veterans, largely from World War II, who were in the dystrophic generation and were attending the hospital clinics. With the exception of one highway supervisor, the patients had menial jobs requiring little responsibility or wit. Six of our patients eventually required economic assistance when their physical handicaps interfered with the satisfactory performance of their work. Of the four cases tested with objective psychological tests, three had I.Q.'s ranging from 75 to 92; four others were described as being dull, with poor memory, impaired calculation ability, inadequate comprehension and lack of insight. None of the patients was sufficiently affected to require permanent institutionalization. Six patients were described as frankly antagonistic, critical and demanding. Often they were aloof and difficult to manage, resenting examination and tests. The superficial gaiety described by Maas and Paterson[27-31] was noted infrequently. However, an inappropriate lack of concern was evident in several patients who had severe physical incapacities and rather poor home surroundings. Apathy and lack of vitality were certainly apparent in the more severely disabled. However, patients with any progressive chronic illness requiring multiple admissions to hospital frequently display reactions to their physical defects in terms of disinterest in outside affairs, irritability and belligerence.

The most striking feature in our group was the apparent social decay with a marginal type of living. It is probable that a combination of factors accounts for this state, heralded by declining physical strength, progressive mental incompetence, and depleted vigour and ambition.

TREATMENT

To date the approach to the treatment of myotonia dystrophia has been unrewarding in view of the failure to co-ordinate the various patterns of the disease into one intelligible explanation. Symptomatic treatment has been the rule. Efforts to date have been directed at reducing myotonic response, improving muscle strength, or removing an opaque lens. With this approach, the patient's distress has been alleviated somewhat, but the progressive course of the disease has not been altered. In the late stages of this condition, supportive management is the only alternative.

Fatalities are usually the result of intercurrent infections or secondary disease processes and are not related to the degenerative processes in the muscle, heart, testicle or lens. The morbidity is high, for it produces weak, despondent, ineffectual people. Perhaps the greatest asset to management is the prophylaxis imposed by the disease itself which yields high proportions of celibates and childless marriages.

Quinine, first introduced by Wolf[48] in 1936, is still one of the most satisfactory therapeutic agents.[22] Of the 11 patients in this series who were given quinine, three showed significant reduction in myotonic symptoms, three had a fair response in terms of evanescent subjective improvement, and two others experienced no improvement at all. In two cases quinine had to be discontinued because of gastric irritation and ringing of the ears. In the other patients, distress from the myotonia was so slight that medication was not warranted. When quinine hydrochloride was given by mouth in doses of 10 to 15 grains twice a day, the early response was generally good; this effect was not well sustained after months of usage.

Procaine amide, in doses of 2 to 4 g., has been found in some cases to be as effective as or more effective than quinine in depressing myotonia.[26, 32] Moreover, it has minimal side effects. Some authors[34, 38] have reported equally beneficial results

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with ACTH and cortisone analogues. Such claims have, however, been challenged,[18, 26, 35] and it would be unwise to employ these drugs on a long-term maintenance basis for a patient with myotonia dystrophia when another therapeutic agent of similar potency could be used.

Potassium-binding resins have been reported to be effective in alleviating myotonia and in restoring normal electromyographic patterns,[43, 44] but such agents are still in a preliminary stage of investigation.

Calcium gluconate diminishes muscle excitability, but its clinical efficacy has not been impressive.[36] Equally unimpressive in counteracting the atrophy or myotonia have been the drugs, aminoacetic acid, adrenaline, and adrenaline with pilocarpine.[47]

Testosterone propionate may improve muscle power,[21] but it is questionable whether the use of androgens improves function in the affected muscle fibres and/or the remaining normal musculature. Long-term therapy with this drug has failed to reverse or halt the course of muscular degeneration.

To date there is no known efficient remedy for dystrophia myotonia.

DISCUSSION

The dichotomy between myotonia and atrophy has been stressed and emphasis has been laid upon their differences in distribution, proportion and importance to the patient. The juxtaposition of myotonia and atrophy appears to be a semantic marriage rather than an interdependent relation. In fact, when muscles are severely myotonic, they are rarely atrophied, and when atrophy is severe, myotonia may be slight or lacking. The onset of myotonia and atrophy is difficult to define, but in this series both were generally found on admission, the prevailing complaint usually being weakness. Cases have been reported in which myotonia was evident without the concomitant presence of atrophy, which accordingly developed at a later date. The reverse, atrophy without myotonia, is rare. The treatment of myotonia is unsatisfactory and unreliable in the total population affected. This poor result is compounded by the fact that patients with myotonia dystrophia infrequently complain of myotonia and are distressed more by the weakness and wasting of their muscles. Quinine and procainamide (Pronestyl) are the most practical and satisfactory drugs for the treatment of myotonia. Efforts to reverse the muscle wasting and creatinuria by use of anabolic androgens or cortisone derivatives have been disappointing. Although myotonia dystrophia is not a lethal disease, early deaths before the age of 50 are common, usually as a result of intercurrent infection or a secondary disease process.

In the search for an all-embracing replacement therapy, attempts have been made to relate the dystrophic process occurring in the lens, heart and muscles to a disorder of the endocrine glands. However, the only constant clinicopathological findings have been those encountered in the gonads. The mild disorders of function of the adrenals, thyroid and pituitary indicated by certain laboratory tests are more apparent than real. The pathogenesis of such disorders has not been accounted for by any consistently encountered, well-defined lesions in the endocrine glands demonstrable at postmortem examination.

Besides the well-documented occurrence of cataracts, blepharoconjunctivitis appears to be the only other ocular manifestation commonly observed. Although four cases of macular degeneration and two cases of bilateral iridocylitis have been described, their significance and association with myotonia dystrophia remains unsettled.

The diffuse myocardial fibrosis encountered at autopsy in one of our cases without atherosclerosis could explain the various conduction defects found in the electrocardiograms of patients with myotonia dystrophia. However, such a deduction cannot be made from such a small number of cases. Further work is necessary to establish the exact nature of the myocardial lesion.

The degenerative effects of this disease are most acutely felt in the scions of those families affected with the gene of myotonia dystrophia. Mental deterioration is a natural product of this disease, and descendants of those affected become progressively more feeble-minded, apathetic and dependent. Social decay is prevalent and is historically documented by these descendants of Ypsilanti.

SUMMARY

Seventeen cases of myotonia dystrophia have been collectively reviewed and discussed to demonstrate the widespread manifestations of this disorder. In those instances where investigations were incomplete or entirely lacking, reference was made to work reported in the literature to provide a comprehensive review of this subject.

I wish to acknowledge my gratitude to Dr. J. C. Richardson, Dr. D. A. Schatz, Dr. R. I. Macdonald and Dr. J. C. Humphrey, for their advice and assistance. I would also like to thank Dr. J. W. Agnos for reviewing the skull films, and Dr. H. P. Brent for the slit lamp photographs.

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CASE REPORTS

ARTERIOVENOUS FISTULA IN AN UNUSUAL SITE*

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ARTERIOVENOUS fistulas are frequently encountered in war-time practice and are usually the result of bullet or shrapnel wounds.[1, 2] Such wounds are less common during peace-time and arteriovenous fistulas resulting from fractures or similar injuries are distinctly rare. Congenital arteriovenous fistulas do occur, but have not been reported in the supra-scapular area.

The purpose of this paper is to report a case of arteriovenous fistula between the right supra-scapular artery and the right subclavian vein with hemodynamic, ballistocardiographic and phono-cardiographic studies before and after surgical correction.

S.W., a 29-year-old white woman, was admitted to the Victoria General Hospital, Halifax, on November 12, 1959, complaining of loss of weight, throbbing headache and shortness of breath. The history was one of good health until March 1959, when she noted that she was losing weight for no apparent reason, since her eating habits and activities had not changed. About this time, she also noticed that climbing stairs and housework, which had previously been well tolerated, were causing shortness of breath and palpitation. The dyspnea continued until the time of admission, but was not progressive. In April 1959, she began to have throbbing headaches, localized to the right side of the head and accentuated by bending over. These occurred at any time of day or night and were not preceded by visual disturbances or followed by nausea. For about two months before her hospital admission, she had noted tinnitus in her right ear, particularly at night, which seemed related to her heartbeat. Also, during the month preceding admission, she noted that her ankles were slightly swollen towards the end of the day.

The functional enquiry revealed a history of menorrhagia, but was otherwise negative. There was a positive family history of tuberculosis and diabetes mellitus (two maternal uncles). At four years of age the patient had had poliomyelitis which left her with residual weakness of the right leg, and at age 12 an Achilles tenotomy was performed. At the age of 10 years, she had fallen on her right shoulder, apparently sustaining a fracture in that region. The exact extent of the injury and whether or not it involved the clavicle are not known.

Physical examination revealed an apparently healthy white woman with obvious wasting and shortening of the right leg. The pulse was 80 per minute and regular. The blood pressure was 125/80 mm. Hg in both arms with the patient recumbent. The radial, brachial, carotid, femoral, posterior tibial and dorsalis pedis arteries revealed normal pulsations. There was a systolic thrill in the right supraclavicular fossa. A continuous machinery-like murmur with systolic accentuation (see phonocardiogram, Fig. 1) was best heard in this area, but was transmitted upward along the right carotid artery and downward over the entire precordium. There was no cardiac enlargement and the heart sounds were normal. Physical examination was otherwise within normal limits.

Her hemoglobin value was 12.2 g. per 100 ml., and her packed cell volume was 42%. The leukocyte count was 5000 per c.mm. with 57% neutrophils and 43% lymphocytes. The urinalysis and serological reaction for syphilis were negative. An electrocardiogram revealed a rate of 94 per minute and low voltage, but

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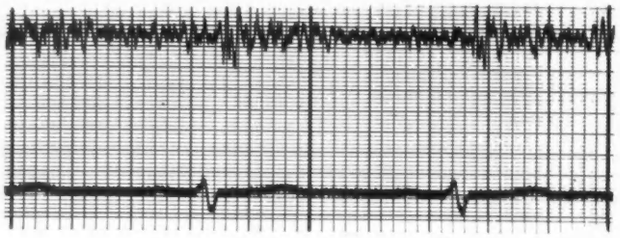

Fig. 1.—Phonocardiogram recorded over the right supraclavicular fossa before operation. Note the to-and-fro murmur.

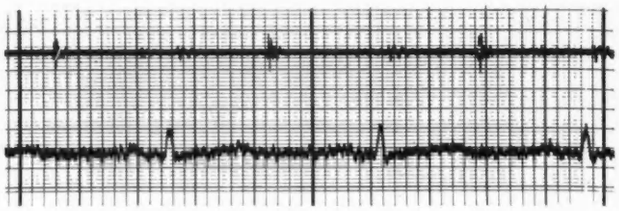

Fig. 2.—Phonocardiogram recorded over the right supraclavicular fossa after operation. The murmur has disappeared.

was otherwise normal. A chest radiograph showed discrete hilar calcifications, with normal heart size and contours.

At this stage the diagnosis was thought to be either arterial aneurysm or an arteriovenous fistula. The weight of evidence was in favour of a carotid or subclavian artery aneurysm, since there were no clinical findings to suggest high cardiac output as would be expected with an arteriovenous fistula. Right heart catheterization appeared therefore to be indicated for the purposes of, firstly, excluding an intracardiac anomaly, secondly, determining the cardiac output and hence the presence or absence of an arteriovenous communication, and, thirdly, performing selective angiocardiography and delineating the arch of the aorta and its major branches.

On November 13, 1959, this procedure was carried out. A No. 7 Cournand catheter was passed into the heart via a left median cubital vein. The oxygen saturation determinations (oximetry), intracardiac pressure values and wave contour assessments were all within normal limits, although the oxygen saturation values of the superior vena cava and the pulmonary artery blood were both somewhat high (see Table I), as might be expected with an arteriovenous fistula in the neck. This resulted in a decrease in the arteriovenous oxygen difference (i.e. the difference between the oxygen saturation of systemic arterial blood and that of the mixed venous blood in the pulmonary artery); the end-result was therefore an increased cardiac output as determined by the Fick method. Cardiac output determined by the dye curve method (pulmonary artery to femoral artery) was also increased (9.3 litres per minute). This was considered to be conclusive evidence of the presence of a left-to-right shunt, and selective angiocardiography was carried out from the pulmonary artery in order to locate the site of the shunt. The result was technically unsatisfactory, and the size and location of the fistula were not determined.

Ultra-low-frequency ballistocardiography performed on November 15, 1959, revealed an abnormally shaped curve, with a cardiac output of only 2.74 l./min. (Figs. 5 and 6). The gross discrepancy between this value for cardiac output and that obtained by the dye method will be discussed later.

The presence of high cardiac output, together with the other findings, was compatible with the diagnosis of an arteriovenous fistula. Because the selective angiocardiogram had not been helpful, the exact location of the fistula was not known, but the physical findings suggested that it was between the right subclavian artery and vein.

On December 16, 1959, operative treatment was undertaken. A transverse supraclavicular incision was made and the fascia and platysma were incised to expose the right internal jugular and subclavian veins and the subclavian artery. A thrill was present over the subclavian artery. Further dissection revealed a communication, ½ to ¾ cm. in diameter, between the suprascapular artery and the subclavian vein. The arterial side of the fistula was excised and the vein wall was repaired. Following this procedure the thrill completely disappeared. The wound was closed in layers.

Postoperatively the murmur had completely disappeared (see phonocardiogram, Fig. 2), and the headaches, tinnitus and dyspnea were no longer present. A repeat dye dilution curve determination (antecubital vein to femoral artery) on March 21, 1960, revealed the cardiac output to be 6.5 litres per minute. Ballistocardiography at this time showed a normal wave form with a cardiac output of 2.06 l./min. The patient made a rapid postoperative recovery and has been asymptomatic since her operation.

DISCUSSION

The occurrence of an arteriovenous fistula between the suprascapular artery and the subclavian vein is very unusual; the authors were unable to find a similar case reported in the literature. Although the exact nature of the trauma to this area is not known, the possibility must be entertained that the lesion was the result of a fracture of the right clavicle or scapula, probably the latter, and not a congenital anomaly. On this basis the lesion would have had to be present for almost 20 years. It is not unusual for an arteriovenous fistula to exist for this length of time without producing cardiac failure.[4] Schenk *et al.*[5] have shown that, in arteriovenous fistulas at any site, the actual flow through the fistula may diminish over a period of time, either as the result of alteration in resistance in the distal portion of the involved artery, or from scar formation and actual contraction of the fistula. This is in disagreement with the opinion expressed by Holman,[6] who feels that there is a progressive increase in blood flow through the fistula. Schenk *et al.*[5] also pointed out that there appeared to be considerable difference between fistulas in the upper part of the body and those in the lower. In the former there seems to be less likelihood of the development of cardiac failure, apparently because of a progressive decrease in proximal arterial flow. Shumacker and Stahl[7] also noted that there was decreased hazard of cardiac failure in fistulas involving the head as compared with those in the lower half of the body. These considerations probably account for the

absence of cardiac failure in the patient reported, for, although the history suggested developing failure, there were no clinical signs to confirm this. There may also be a relation between these observations and the ballistocardiographic findings (see below).

The hemodynamic studies are illustrated in Table I. The cardiac output and cardiac index were increased, as would be expected. These increased values argue against the presence of significant cardiac failure, since Muenster, Graettinger and Campbell[4] have shown that, as these patients develop failure, the output falls.

TABLE I.—HEMODYNAMIC DATA

	Before surgery	*After surgery*
Systemic arterial blood pressure	125/80 mm. Hg	120/80 mm. Hg
Pulmonary arterial blood pressure	30/14 mm. Hg	
Cardiac output (dye curve)	9.3 l./min.	6.5 l./min.
Cardiac output (ballistocardiogram)	2.74 l./min.	2.06 l/min.
Body area	1.6 sq. m.	1.6 sq. m.
Cardiac index	5.4	4.0
Superior vena cava oxygen saturation (oximetry)*	75%	
Pulmonary arterial oxygen saturation* (Van-Slyke)	83.5%	
Systemic arterial oxygen saturation (Van-Slyke)	97.5%	
DYE CURVE DATA		
Appearance-to-manifest recirculation time	14 sec.	16.5 sec.
Mean recirculation time	15.5 sec.	16.5 sec.

*Note: The apparent discrepancy between these two values is due to differences in methods of determination.

Although one cannot compare the shape of the dye curves because of the differences in injection site, they do illustrate several interesting points (Figs. 3 and 4). In the first place, the preoperative cardiac output calculated by the forward triangle method was 9.3 litres per minute as compared to 6.5 litres per minute postoperatively. The relatively high postoperative value was probably due to excitement. Secondly, the re-circulation hump of the preoperative curve is of relatively low amplitude, suggesting some re-circulation. There was also a difference between the appearance-to-manifest re-circulation time of 2.5 seconds, although the mean re-circulation time varied only by one second. These results are similar to those of Scheiner *et al.*[8]

The ballistocardiograms (Figs. 5 and 6) are most interesting in that the prominent downward (J) deflection in the preoperative tracing suggests an increased flow of blood in the direction of the head, as one would expect in this condition. It has also been noted earlier that the values for cardiac output by the dye-curve method were completely at variance with those obtained by ballistocardiography (i.e. 9.3 l./min. as compared with 2.74 l./min. preoperatively and 6.5 l./min. as compared with 2.06 l./min. postoperatively). It has been suggested that the ballistocardiogram mirrors increased blood flow in the direction of the legs but not in the direction of the head. For example, there is a report in the German literature[9] in which a patient with an arteriovenous fistula in one leg had very closely correlated cardiac output measurements as determined by the Fick method and by ballistocardiography; and the lack of correlation between cardiac output determinations by the Fick or dye-curve method and these determinations by ballistocardiography in various congenital cardiovascular anomalies has been corro-

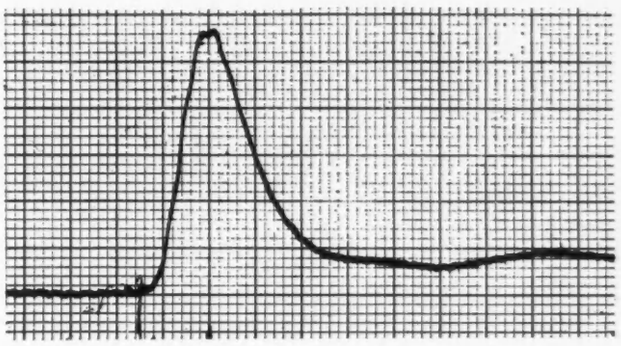

Fig. 3.—Dye dilution curve with injection into pulmonary artery and sampling from femoral artery. Recorded before operation (Cardiogreen).

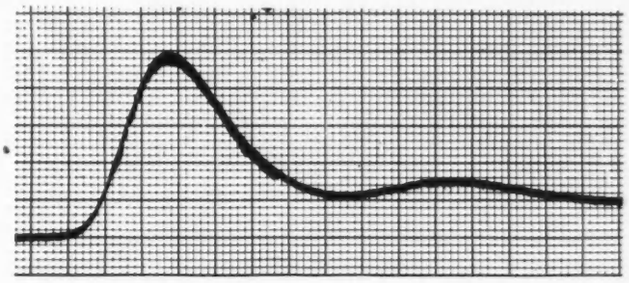

Fig. 4.—Dye dilution curve: injection was into the antecubital vein and sampling from the femoral artery. Recorded after operation (Cardiogreen).

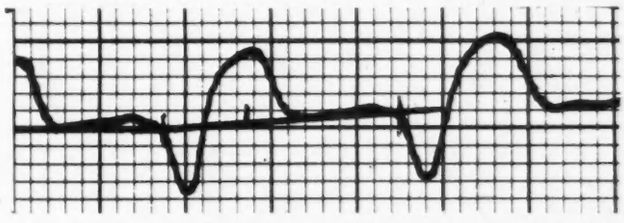

Fig. 5.—Ultra-low-frequency ballistocardiogram. Recorded before operation. Note the prominent downward J deflection.

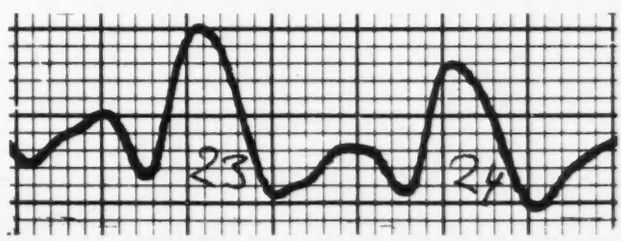

Fig. 6.—Ulta-low-frequency ballistocardiogram. Recorded after operation. Note normal contour.

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borated at this centre.[10] The ballistocardiogram therefore might very well reveal evidence of increased cardiac output, as measured by the Klensch formula, in the presence of an arteriovenous fistula in a lower extremity, but not when such a fistula is in an upper extremity, or in the head or neck. In such cases, the figure for cardiac output as calculated by this formula may even be diminished.

The phonocardiogram (Fig. 1) demonstrates the murmur and illustrates the systolic accentuation, which in some cases seems to impart a to-and-fro character to the murmur. This finding is similar to that reported by Edwards and Levine[3] and is typical of the murmur of an arteriovenous fistula.

Fig. 2 is the phonocardiogram from the same area recorded postoperatively and shows no murmur. The primary cause of the murmur of an arteriovenous fistula is the gradient from the high-pressure arterial side to the low-pressure venous side. This results in a rapid flow through the fistula with consequent vibration of the vessel wall and the production of sound.[3] The systolic accentuation is, of course, due to the increased flow during systole.

SUMMARY

A case of an arteriovenous fistula between the right suprascapular artery and the subclavian vein is reported. Phonocardiography demonstrated a continuous murmur with systolic accentuation in the supraclavicular fossa that disappeared after operation. Ballistocardiography revealed the presence of a prominent J wave before operation that became normal after repair of the fistula. Hemodynamic studies revealed a decrease in the difference between the oxygen saturation of femoral artery blood and that of the mixed venous blood in the pulmonary artery, as might be expected in an arteriovenous fistula. The cardiac output was increased but the pressures and wave-forms in the right cardiac chambers were normal. All of the abnormal findings disappeared after surgical correction of the fistula.

The authors are deeply indebted to Dr. W. Josenhans, Department of Physiology, Dalhousie University, Halifax, N.S., for all the work involving ballistocardiography performed in this study, and for much information regarding the theoretical concepts underlying this procedure.

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RENAL TUBULAR ACIDOSIS

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THE SYNDROME of renal tubular acidosis was first described by Lightwood[1] in 1935 and by Butler, Wilson and Farber in 1936.[2] Cases have been reported in infants[1-4] and in adults;[5-7] and there may be a familial incidence,[8] suggesting that some cases are of congenital origin. The disorder may occur as a solitary defect or with other renal tubular diseases such as glycosuric osteomalacia, the Fanconi syndrome, Lowe's syndrome and inborn errors of metabolism such as cystinosis, galactosemia, Wilson's disease, nephrogenic diabetes insipidus and perhaps vitamin D deficiency.[9]

Renal tubular acidosis is a syndrome characterized by a sustained systemic metabolic acidosis due to a disorder in function of the renal tubules, although the pH of the urine appears to range from neutral to about 7.5 and the blood plasma shows a decreased bicarbonate and usually a high chloride concentration. Glomerular function is normal or shows evidence of minimal insufficiency. Osteomalacia may develop without disturbance in serum calcium or phosphate levels. Renal calculi are frequent and many cases show some degree of nephrocalcinosis.[10] There may be isolated episodes of muscle weakness associated with hypokalemia in some cases.[9, 11]

This case is reported because the condition appears to have developed in adult life and there may have been several etiological factors.

A Caucasian woman born in 1908 was well until 1931, when she had a right nephrectomy because of a calculus in the right ureter. This was followed by acute anuria, and the surgeon split the capsule of the left kidney, which brought about restoration of renal function. Since then she has had many illnesses and hospital admissions. Hospital admissions from 1936 to 1953 were: four for acute Addisonian crisis; one for a fractured pelvis; one for intestinal obstruction; one for an oophorectomy; one for an appendectomy; and one for a fractured tibia. The urinalysis on these nine admissions was acid in reaction. She was treated at home during this period for one Addisonian crisis; two attacks of renal colic, with passage of calcium oxalate stones, and once for lobar pneumonia. She received penicillin for the latter and was never given sulfonamides.

In 1954 she complained of abdominal cramps and loose stools. Radiological examination of the stomach and duodenum was negative. The terminal five to six inches of the ileum presented flattening of the mucosal pattern, some narrowing of the lumen and lack of expansibility and contractility. Barium enema examination indicated that the ileocecal valve was incompetent, the barium passing back into the terminal ileum for a distance of about 18 inches. The terminal ileum appeared to be involved in an old inflammatory process with loss of valvular markings. The ileocecal valve was fixed in an open position. There was marked shortening of the whole colon, with no haustral markings and no contractility.

The patient was hospitalized in 1955 because of ulcerative colitis, and in 1957 she underwent a gastrectomy (two-thirds of the stomach was resected) for a gastric and a duodenal ulcer. The urine was acid in reaction in 1955 but was alkaline in 1957.

In 1958 she was again hospitalized, because of a perforation of the ileum; 13 inches of the ileum was resected and the pathological diagnosis was regional ileitis. Some of the laboratory data at that time were as follows:

September 9, 1958.—Serum sodium was 142 mEq./l.; potassium, 3.1; chloride, 102; and carbon dioxide combining power, 24.2. Non-protein nitrogen value was 40 mg. %. Urine pH was 7.5.

September 29, 1958.—Serum sodium value was 144 mEq./l.; potassium, 5.1; chloride, 109; carbon dioxide combining power, 21. A 17-ketosteroid value was 5.7 mg. (cortisone had been discontinued two weeks before the test).

In 1959 she suffered from weakness, loss of weight and loose bowel movements. Results of radiological examination of the colon were unchanged from that in 1954 and the stomach showed partial gastric resection. This illness was diagnosed as a malabsorption syndrome secondary to gastric resection and regional ileitis. The patient was given cortisone 12½ mg. daily, which she had taken periodically for varying periods since 1951.

In January 1960 there were further weight loss, marked weakness and diarrhea. Results of laboratory investigation were as follows: Hemoglobin value was 64%, red blood cell count 3,500,000; white cell count 5000 per c.mm. Differential count revealed 71% neutrophils, 19% lymphocytes, 3% eosinophils and 7% not identified. Hematocrit value was 31%. Smear examination revealed slight macrocytosis, polychromasia, bizarre forms, target cells, and spherocytes. The red blood cells appeared normochromic. Platelets were normal in number, an occasional giant one being seen. Total serum protein value was 6 g.; A/G ratio was 1:37. Albumin was 53.7%; α_1 globulin, 5.4%; α_2 globulin, 9.9%; β globulin, 9.4% and 7.9%; and γ globulin, 13.8%. Serum sodium value was 136 mEq./l.; potassium, 4.2; chloride, 102; carbon dioxide combining power 13.7. Non-protein nitrogen value was 42 mg. %, and serum calcium 9.3 mg. %.

In February 1960 the patient fell and fractured her left humerus at the wrist, as well as the condyle of the left femur. Radiologically the bones showed considerable decalcification.

In April 1960 further laboratory investigation revealed the following: Urine specific gravity was 1.020 and urine pH 6.0. Urine analysis for albumin and sugar was negative. Microscopic examination revealed oxalate crystals. Urine citrate value (24-hour specimen) was 25 mg. % (normal 200-1250).[12] Serum sodium value was 135 mEq./l.; potassium, 4.3; chloride, 111; carbon dioxide combining power, 15.3. Alkaline phosphatase was 9.5 King-Armstrong units; serum phosphorus, 3.7 mg. %; serum calcium, 8.9 mg. %. Non-protein nitrogen was 40 mg. % and blood glucose 70 mg. %. Blood pressure readings varied between 80/55 and 110/70. Review of past radiographs did not disclose any nephrocalcinosis.

The following diagnoses were made: renal tubular acidosis with osteomalacia, Addison's disease, malabsorption syndrome secondary to regional ileitis and partial gastrectomy, and chronic ulcerative colitis.

The following treatment was prescribed: (1) a preparation consisting of potassium citrate 216 g., sodium citrate 196 g., citric acid 100 g., syrup of orange 400 c.c., and water to make 2000 c.c. The patient was directed to take 15 c.c. in water four times a day. (2) Cortisone, 25 mg. daily. (3) Ferrous succinate, grains 5, three times daily. (4) Multiple vitamins. (5) Low roughage, high protein diet. (6) Norethandrolone (Nilevar), 10 mg., three times daily.

DISCUSSION

A case of renal tubular acidosis is reported in a 50-year-old woman who had only one kidney. There was no family history of recurrent renal calculi, kidney disease or recurrent fractures. The patient had many hospital admissions and over a period of 10 years her urine was always acid in reaction, suggesting that she did not have the syndrome at that time. She had some decalcification of her skeleton which was possibly due to the renal tubular acidosis, the result of taking cortisone, and to her age. There was no evidence of nephrocalcinosis and no history of pyelonephritis or use of sulfonamides. This patient was subjected to much stress: major surgery, fractures, acute infections and Addisonian crises, over a period of 25 years. She took Placidyl tablets (tranquillizer) on occasion, which, clinically, appeared to worsen her condition. A case has been reported in which the patient was addicted to paraldehyde and suffered from renal tubular acidosis and when the addiction was cured the renal tubular function appeared to be normal without any therapy.[13]

SUMMARY

A case of renal tubular acidosis is reported which appeared to be an acquired defect or a latent congenital defect which developed after many years of repeated stress in association with Addison's disease.

I am grateful to Dr. A. Rapoport for his assistance and for measuring the urine citrate.

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THE CANADIAN MEDICAL ASSOCIATION
JOURNAL
LE JOURNAL DE
L'ASSOCIATION MÉDICALE CANADIENNE

published weekly by
THE CANADIAN MEDICAL ASSOCIATION
Editor, C.M.A. Publications:
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THE INTERNATIONAL STATISTICAL CLASSIFICATION OF DISEASES, INJURIES AND CAUSES OF DEATH

THERE continues to be some uncertainty as to the significance of The International Statistical Classification of Diseases, Injuries and Causes of Death, published by the World Health Organization,[1] and its place in the field of hospital recording. The publication recently by the United States Public Health Service of an adaptation of this Classification for indexing of hospital records[2] seems to have added to the consternation.

The International Statistical Classification of Diseases is designed for the tabulation of the causes of sickness as well as the causes of death; it is a step toward the improvement and the increased usefulness of morbidity and mortality statistics; it meets a need in all countries where studies of the causes of sickness and death are undertaken.

Continuing enquiries from hospitals and persons interested in or responsible for indexing and classifying disease and injury have indicated that there is some confusion concerning the respective functions of the International Statistical Classification and the Standard Nomenclature of Disease, and a feeling that there is conflict between the two. To recognize that there is no conflict and no real overlapping, it is necessary to understand the precise nature and purpose of these two publications.

The International Statistical Classification of Diseases and the Standard Nomenclature of Disease serve two distinct purposes. The International Statistical Classification is designed to establish international uniformity in the compilation of statistics on the causes of sickness, injury and death. It is a *statistical* list and therefore is much less detailed than is the Standard Nomenclature. It comprises 612 main categories of disease conditions, 153 categories for the classification of the external causes of injury, and 189 categories for the nature of injuries.

The Standard Nomenclature is a *dictionary* of accepted medical terms; it is designed to standardize the diagnostic terminology used by physicians and to facilitate the indexing and filing of hospital records generally. The fineness of diagnosis breakdown in the Standard Nomenclature is, therefore, much greater than it is in the International Statistical Classification, and it contains many thousands of entities.

The Standard Nomenclature is widely used as the authoritative medical nomenclature; it has no significant competitor on this continent and there is no prospect that any other may replace it. This Nomenclature is under continuing revision and provides cross-reference code numbers to the International Statistical Classification to facilitate statistical studies on an international and comparable basis.

The distinction, both in nature and in function, between a nomenclature and a statistical classification is effectively described in the Preface to Volume I of the Manual of the International Statistical Classification itself.

> "Basically, a medical nomenclature is a list or catalogue of approved terms for describing and recording clinical and pathological observations. To serve its full function, it should be extensive so that any pathological condition can be accurately recorded. As medical science advances, a nomenclature must expand to include new terms necessary to record new observations. Any morbid condition that can be specifically described will need a specific designation in a nomenclature.
>
> "This complete specificity of a nomenclature prevents it from serving satisfactorily as a statistical classification. When one speaks of statistics, it is at once inferred that the interest is in a group of cases and not in individual occurrences. The purpose of a statistical compilation of disease data is primarily to furnish quantitative data that will answer questions about groups of cases.
>
> "A statistical classification of disease" [on the other hand] "*must be confined to a limited number of categories*" [italics ours] "which will encompass the entire range of morbid conditions. Categories should be chosen so that they will facilitate the statistical study of disease phenomena. A specific disease entity should have a separate title in the classification only when its separation is warranted because of the frequency of its occurrence or its importance as a morbid condition justifies its isolation as a separate category . . . Every disease or morbid condition, however, must and does have a definite and appropriate place as an inclusion in one of the categories of the statistical classification . . ."

The purpose of a statistical classification "is to provide a list of disabilities for compiling statistics and not a nomenclature of diseases and injuries". Not every condition receives a particular number in a statistical list, but there is a category to which every disease, condition or injury can be referred, and this is achieved by grouping. In the International Statistical Classification the conditions which should be set up as separate categories are

determined on the basis of frequency, importance, and specificity of the entities concerned.

There are three requirements in the field of hospital records and statistics—naming diseases, indexing diagnoses, and preparing statistics. Many have regularly regarded the Standard Nomenclature as serving effectively all three needs. It has been emphasized many times by experts both in Canada and elsewhere that this is not entirely so, but it is still necessary to draw attention to the fundamentals which are involved.

The Standard Nomenclature was not developed to serve statistical purposes; its great function lies in standardizing individual diagnoses and in facilitating indexing and filing. The International Statistical Classification can never be substituted for the Standard Nomenclature, for it is designed to meet needs *for grouping diagnoses*. It is flexible enough, however, that it may be extended to provide whatever degree of detail is desired, not only for statistical analyses but for indexing purposes as well.

The basic conflict appears to be in the establishment of an index for filing records. In some quarters it is felt that the Standard Nomenclature should be used for indexing and filing purposes, and it is being widely used for that purpose. Others feel that the Standard Nomenclature should be used for naming diseases and is not satisfactory for filing and indexing purposes. This difference of opinion may be reconciled by adapting the International Statistical Classification to provide a convenient diagnosis cross-index, and an attempt has been made recently to do this.[2] Such a diagnosis cross-index would not, of course, supplant the Standard Nomenclature *as a nomenclature* but, as a diagnosis cross-index, it would be complementary to it.

Current general policy and practice is to adopt the Standard Nomenclature as the dictionary of approved medical terms. Doctors will then be committed to use it in making their diagnoses. When the clinical records are passed to the medical records department of the hospital, they can then be coded for indexing purposes according to the Standard Nomenclature or to an adaptation of the International Statistical Classification. Statistics for publication can best be prepared according to the International Statistical Classification or an appropriate modification thereof.

The following is a quotation from the introduction to the International Classification of Diseases Adapted for Indexing of Hospital Records, published by the U.S. Department of Health, Education and Welfare, Public Health Service:[2]

> "Because this is a classification of diseases and in no sense a nomenclature of correct terms, the International Classification of Diseases should not be given to doctors as a guide in expressing their diagnoses. There is still need for doctors to phrase diagnoses correctly and in a uniform manner according to the Standard '(or other approved)' Nomenclature to ensure accurate coding by this International Classification."

There is thus no need for conflict between the Standard Nomenclature of Disease and the International Statistical Classification of Diseases, Injuries, and Causes of Death. The two cannot be used interchangeably, for they are designed to serve different purposes. The uncertainty which persists is due to a failure to recognize the precise functions of the two publications. The simplest way of resolving the problem is to regard the Standard Nomenclature as a dictionary of approved terms and diagnoses and the International Statistical Classification as the approved statistical list for tabulating data; either one can be used for indexing of hospital records. A.H.S.

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CURRENT CONCEPTS IN THE TREATMENT OF PARKINSONISM

THE distressing and pathetic physical and psychological incapacity created by parkinsonism is posing an ever-increasing therapeutic problem in today's medical practice. In the United States alone, there are over 1,000,000 victims of this disease, and the incidence of new cases is increasing.[1] It has been said that in its early phases parkinsonism is one of the easiest ailments to treat because of its slow progression and frequent stationary periods that may last as long as 5 to 10 years.[1] Early and intensive treatment can relieve or modify the symptoms of rigidity and tremor in many instances. If the condition is neglected, however, the disease progresses and the crippling manifestations of contracture, deformity and disability develop in later years as a result of secondary atrophy due to the failure to utilize rigid muscles to maximum advantage.

During the past ten years research in this disease has yielded some encouraging results. Lesions have been demonstrated in the globus pallidus, substantia nigra and red nucleus, and one may assume that there is an abnormal neural circuit within the central nervous system that causes tremor and rigidity.[2] In the field of medicinal therapy, natural products derived from plants have been largely replaced by synthetic drugs, since the latter are much easier to administer and can be created in the laboratory in large numbers, thus affording better opportunity to select those with the least disturbing reactions and the greatest impact on symptoms. In addition to the fact that they are very limited in number and therefore in their range of activity, some of the natural products, such as atropine and belladonna solutions, involve a certain

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degree of hazard of glaucoma, especially when used in elderly patients. Hyoscine, however, is still used to good advantage in the control of tremor, for patients who can tolerate it.

The newer synthetic drugs include trihexyphenidyl (Artane), cycrimine (Pagitane), procyclidine (Kemadrin), biperiden (Akineton), benztropine (Cogentin), ethopropazine (Parsidol), chlorphenoxamine (Phenoxene) and orphenadrine (Disipal). In addition to their advantages over the plant derivatives each synthetic drug has certain advantages over the other synthetic products: some are more effective against tremor than against rigidity; some relieve muscular rigidity more effectively; and some have fewer and/or less severe side-reactions than others.

In addition to these "anti-parkinsonian" drugs, many preparations employed in the treatment of other diseases occasionally prove effective against one or another of the symptoms of Parkinson's disease. Antihistaminics, cerebral stimulants, diuretics, rauwolfia alkaloids, barbiturates, tranquillizers, antidepressants, alcohol and vitamins may all be useful in some individual cases.

Others, not so sanguine in their views concerning the efficacy of medical management of this disease, hold the opinion that although drug treatment relieves muscular rigidity for a while and occasionally modifies tremor, the disease usually progresses undeterred.[2] Accumulating experiences with the various early and more recent operative procedures appear to indicate that strategic interruption of the pallidofugal fibres, the ansa and the fasciculus lenticularis, constitute an effective surgical means of alleviating the rigidity and tremor of parkinsonism.

Beginning in 1955, in Edinburgh, Gillingham[2] instituted an investigation designed to determine the ideal site and size of surgical lesion which would provide maximum relief and sustained improvement. To study the effect of electrocoagulation lesions in the globus pallidus, internal capsule and thalamus, separately or in combination, he systematically assessed 126 patients before, during and after operation (a modified form of Guiot's stereotaxic method); and finally, he carried out an extended follow-up study of up to five years and not less than six months. From the results obtained in the four phases of this study, each phase involving a different lesion or combination of lesions, it appeared that tremor and rigidity were controlled most effectively by the strategic interruption of the thalamopallidal connections, essentially the ansa and the fasciculus lenticularis. It is not yet clear, however, whether this can best be achieved in the capsule by a relatively small lesion or in the adjacent thalamus and globus pallidus. Of the first 60 unselected patients, 88% had their tremor and rigidity abolished or significantly relieved in the limbs of the treated side, without complications. In the subsequent 66 patients, a minor degree of selection was practised. Most were treated by combined ipsilateral lesions in the thalamus and pallidum adjacent to the internal capsule, but eight patients had lesions deliberately created within the capsule. All showed benefit, and approximately 90% were greatly relieved. Complications were minimal, and there were no operative deaths. In the overall series of 126 patients, 22 had bilateral lesions created, and only the first three showed any psychological impairment following the production of large lesions. As a result of these experiences, selection of patients on the basis of age and of the degree of widespread manifestations of parkinsonism as judged preoperatively, was recommended. In patients with widespread disease and/or in patients over 65 years of age, the dangers of accentuating intellectual deterioration are more pronounced. Nevertheless, results are still somewhat unpredictable and the most dramatic response occasionally occurs in the most disabled patient.

Even though great advances have been made in the surgical treatment of Parkinson's disease, it is still not known whether the progress of this relentlessly progressive disease can be halted by operative procedures. However, there are indications that this may be achieved by strategically placed lesions of adequate size. There are still some aspects of the disease that are not appreciably helped by the surgical procedures at present in use: these include oculogyric crises, loss of voice volume, festinant gait and excessive salivation.

Although both the medicinal and surgical treatments of parkinsonism have improved greatly during the past decade, it is evident that a completely satisfactory treatment has not yet been found. While the burden of care of the parkinsonian patient falls on the physician, the full co-operation of the patient is essential if the best possible results are to be obtained. Physiotherapy and occupational therapy, in particular, can do much toward the prevention of contractures and disabilities, and the correction of ingrained bad habits due to rigidity in posture, gait and fine movements. F.L.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

The essential and primary object of literary and scientific societies and associations is the advancement of science and letters, and the mutual improvement of the members. It may be questioned if any class stand in greater need of such reunions than medical men. The reasons are obvious. Of all men the medical man needs clearness of vision and soundness of judgement. Alone and unaided, we are called upon to decide complicated problems, involving the well-being, even the lives, of our fellow-men. The methodical recording of our experiences and the preparation of papers is an education.—G. E. Armstrong: The President's Address to the Canadian Medical Association, 1911, *Canad. M. A. J.*, 1: 591, 1911.

Letters to the Journal

IN VITRO SENSITIVITY OF ROUTINE HOSPITAL PATHOGENIC BACTERIA TO A GROUP OF COMMONLY USED ANTIBIOTICS

To the Editor:

I have read the short communication by Dr. L. Whitaker (*Canad. M. A. J.*, 84: 1022, 1961) reporting his experience with sensitivity discs, and his conclusions are disturbing because I think that they are based on a mathematical illusion. It would appear from his article that the combination of novobiocin and tetracycline (Albamycin-T) has some inherent superiority over single antibiotics. This apparent superiority can be completely explained by a simple mathematical additive effect. *Organisms resistant to one and sensitive to the other would be sensitive to the combination.* May I illustrate. I went over our own files for the month of January 1961 and tabulated the disc sensitivity results for all the coliform organisms tested with both novobiocin and oxytetracycline. Albamycin-T discs were not used. I have calculated the theoretical sensitivity pattern to the Albamycin-T discs by assuming the above hypothesis to be true. This figure should give the minimum number of strains that would be sensitive to the combination if *only* an additive effect were seen. In every case where the organism is sensitive to only one of the pair, it is reported sensitive to the combination, and in such instances the one antibiotic only of the pair would be of any effect if used for therapy and the other one would, at best, be wasted.

SENSITIVITIES OF EACH STRAIN TO EACH ANTIBIOTIC

Coliform strain No.	*Novobiocin*	*Oxytetracycline*	*Albamycin-T* (see below)*
1	—	—	—
2	+	—	+
3	—	+	+
4	+	—	+
5	—	—	—
6	+	+	+
7	—	—	—
8	+	+	+

Totals: Eight strains tested + = 4 = 50% + = 3 = 37.5% + = 5 = 62.2%

*Theoretical results if only an additive effect were operative.

The figures speak for themselves. If this additive effect is not removed from the figures reported in the article, they become meaningless and the author's conclusions are unwarranted.

I realize that the tetracycline in Albamycin-T is not oxytetracycline, but this does not negate the basic hypothesis. You could get similar figures with any combination of antibiotics if the organisms differed in their sensitivity to the individual members of the combination.

I think it is most unfortunate that such uncritical work is published. It certainly does not add to the stature of our Journal.

1221 Avenue J, North,
Saskatoon, Sask.

H. J. BLOCK, M.D.,
Pathologist.

To the Editor:

Dr. Block has drawn to our attention the possibility of an additive effect to explain the apparent superiority of Albamycin-T. His table using eight strains certainly seems to support this. However, a review of our tests indicates that there is a number of organisms which are sensitive to neither novobiocin nor oxytetracycline, but are sensitive to the combination.

I should like to thank Dr. Block for his remarks and would appreciate learning later of his experience with a larger number of strains, not only of coliforms, but of other organisms which are isolated in his routine bacteriological service.

LORNE WHITAKER, B.A., M.D.,
Director of Laboratories.
St. Catharines General Hospital,
St. Catharines, Ontario.

GAS GANGRENE FOLLOWING PERFORATION OF THE ALIMENTARY CANAL

To the Editor:

The anaerobes are much neglected organisms, and Dr. M. D. Silver[1] does a valuable service in pointing out that clostridial infections may follow perforations of the alimentary tract. Although it is true, as Dr. Silver states, that clinically obvious gas gangrene is rare when compared with the frequency of gastrointestinal perforations, I think that an unrecognized infection with the patient's own large bowel clostridia may be the immediate cause of death in a number of seriously debilitated patients.

I have seen several cases at autopsy which showed hemorrhages and bubbles of gas in liver, spleen, and on occasion in the myocardium, although the body was examined soon after death and refrigerated until examined. These lesions contained numerous *Clostridium welchii* and in some cases showed a polymorphonuclear infiltration. Many pathologists disregard these appearances and take neither histological sections nor bacteriological cultures from the affected tissues, since they consider them always to represent mere postmortem bacterial invasion. I think it likely that these postmortem findings in fact sometimes arise as the result of a terminal clostridial septicemia. In the presence of a failing circulation and anoxic tissues, clostridia escaping into the blood stream from the colon, which in these cases is often involved in a neoplastic process, may localize in various widely separated organs. The clostridium I isolated in these cases was *Cl. welchii*, and this may correlate with the ability of this organism to grow well in microaerophilic as well as in completely anaerobic conditions.

Blood cultures were not taken during life in any of the cases I saw, so that the occurrence of a *Cl. welchii* septicemia can only be postulated. However, four cases of leukemia have been reported[2] in which clostridia were isolated from the blood before death. In three the clostridial septicemia was terminal and in one it was successfully treated with penicillin one month before

the patient died of another complication. It seems probable that this condition is not recognized because anaerobic blood cultures are seldom considered in these circumstances. In most cases the diagnosis would be of purely academic interest but there are rare cases where diagnosis and treatment might tide a patient over an acute severe illness with a hopeful long-term prognosis.

I. B. R. DUNCAN, M.B., Ch.B.,
Assistant Professor of Bacteriology, University of Western Ontario.

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MEDICAL NEWS IN BRIEF

SEROLOGICAL REACTIONS IN RHEUMATOID ARTHRITIS

An annotation in the *British Medical Journal* (1: 1097, 1961) has recently made a review and an evaluation of the place of the Rose-Waaler test in the care of patients with rheumatoid arthritis. The Rose-Waaler test with its numerous modifications, including the latex fixation and the bentonite flocculation tests, tests for the presence of a specific macroglobulin in the serum of most patients with rheumatoid arthritis (and some other persons). It is generally agreed that it is of antibody-like nature specifically directed against antigenic groups shared by many species of globulin, and, as a corollary, that "the rheumatoid subject is apparently capable of recognizing and therefore regarding as foreign a degree of change in an autogenous protein that is ignored by the immunological mechanism of normal individuals". However, it has been found that: (1) some patients with rheumatoid arthritis, as defined by strict clinical criteria, fail to give a positive titre in these tests; and (2) there is a high incidence of, apparently, rheumatoid arthritis in patients with congenital agammaglobulinemia.

In a recent study, in-patients who met all the clinical criteria for rheumatoid arthritis but who had a sero-negative reaction were reviewed after an average follow-up period of 5.4 years. During this period, discovery of other factors had led to 11 patients being classified under another heading, and in all of these the Rose-Waaler test had remained negative. Of the 45 patients who still met the criteria for rheumatoid arthritis, the Rose-Waaler test became positive in 10: the remainder showed negative titres and most of them showed clinically typical disease with symmetrical peripheral polyarthritis. Although several authors have commented on the worse prognosis of patients with sero-positive rheumatoid arthritis, in this series the only three fatalities in those classified as rheumatoid arthritis at follow-up were in the still sero-negative subgroup. Perhaps given more time these cases might have "converted", since this process may take up to 23 years.

The main conclusions drawn are that the sheep-cell agglutination test is valuable in research, and a negative result should alert one to possible mis-diagnosis; but for the individual patient the test is not, at present, a reliable guide to prognosis and treatment. Since it has been found that there is a decrease in Rose-Waaler titre in patients with rheumatoid arthritis on gold treatment and an increase in titre in those on prednisone treatment, the test may have some implications for therapy.

MATERNAL RUBELLA AND CONGENITAL HEART DISEASE

Since the first report of the clinical observation that maternal rubella in early pregnancy was followed by congenital cataract and malformations of the heart, many investigations have been carried out concerning the relationship of maternal rubella to congenital heart disease and to other congenital defects. Campbell (*Brit. M. J.*, 1: 691, 1961) has made a comprehensive study of these various investigations and has attempted to answer four questions concerning this relationship: (1) What is the risk to the child after maternal rubella during pregnancy? (2) When the heart is affected, what malformations are most common? (3) What proportion of congenital heart disease as a whole is due to maternal rubella? and (4) How important are other infections (viral or bacterial) in causing congenital malformations?

The investigations reviewed indicate that the risk of abortion and of malformations in the child after maternal rubella during the first 12 weeks of pregnancy is considerable, but that the risk must still be expressed as lying between wide limits: between 30% and 70% during the first four weeks; between 25% and 55% during the second four weeks; between 20% and 40% during the third four weeks; and between 10% and 25% during the fourth four weeks. Beyond the fourth four weeks of gestation there is no increased risk. It is suggested that perhaps the lower figures are closer to the true risk generally and the higher ones apply to particular epidemics.

The greatest risk is that of deafness, then of congenital heart disease and then of cataract; mental defect, microcephaly and several other malformations occur with lesser frequency. All of these defects may occur alone or in combination. Of the cardiac malformations, persistent ductus is the most common (58%), followed by ventricular septal defect (18%); in about 6% the two defects are combined. Atrial septal defect, pulmonary valvular stenosis and the tetralogy of Fallot each occur in approximately 6% of cases. This distribution is unlike that found under other conditions. Maternal rubella is responsible for some 2% to 4% of all cases of congenital heart disease. The proportion of *all these* caused by maternal rubella and all other viral infections was thought to be less than 10% (Congress on Congenital Malformations, July 1960). Although other viral infections, including mumps, measles, epidemic hepatitis and poliomyelitis, may be associated with similar malformations, it appears unlikely that they often are. Further investigations are needed, however, concerning the effects of measles and even minor infections during pregnancy.

(Continued on advertising page 12)

THE NINETY-FOURTH ANNUAL MEETING OF THE C.M.A.

SCIENTIFIC PROGRAM: TEACHING SESSIONS

Tuesday, June 20

"SOME INTERESTING ASPECTS OF ENDOCRINOLOGY AND NUTRITION"

Chairman: *Dr. D. R. Wilson*, Edmonton
Panelists: *Dr. P. B. Rose*, Edmonton
Dr. C. Hollenberg, Montreal
Dr. J. Ducharme, Montreal

The Chairman, DR. D. R. WILSON, Professor of Medicine, University of Alberta, opened this teaching session by describing it as a discussion of the various endocrinologic and nutritional problems that a practitioner was likely to see in his office. The format was that each problem with its history and physical findings was introduced by "the family physician in his office," in this case Dr. P. B. Rose of Edmonton, followed by a discussion of the best way to handle the matter by the other members of the panel.

The first case was as follows.

A 36-week infant weighing 4½ lb. was delivered by Cesarean section after 18 hours of labour. The mother had a history of receiving norethindrone (Norlutin) in the dose of 10 mg. per day for 16 days on two occasions during her pregnancy in order to avoid abortion.

It was felt that the diagnosis was female pseudohermaphroditism due to female hormone but that the differential diagnosis lay within the broad classification of: (a) fetal (primary adrenal virilism), (b) maternal, (c) iatrogenic, and (d) others.

By investigating the urinary hormone excretion and sex chromatin pattern a definitive diagnosis can usually be made in the neonatal period. It is important for both parents and the future of the infant that the sex be defined as quickly as possible. In the case of iatrogenic female pseudohermaphroditism, the infant will usually "grow up to the clitoris", or with minor plastic repair will grow normally and bear children. The simple way of determining sex, where this type of problem is encountered, is to have the family physician take a buccal smear himself, by a very simple technique, and send the smear to one of the larger centres for interpretation.

In the second case described, an 8-year-old boy with bilateral cryptorchidism had been treated during his eighth year by gonadotrophic hormone with resulting precocious puberty.

There was no doubt in anyone's mind that his was an iatrogenic precociousness, and there was a general feeling amongst the panel that no treatment at all should be instituted in these cases until the immediate pre-puberty period. Dr. J. Ducharme of l'Hôpital Ste-Justine felt that all that should be prescribed at that time was a short course of gonadotrophic hormone, 5000 to 10,000 units, over a few days and then to wait for approximately two weeks; if the testes had not descended by this time, an operation should be performed. Dr. C. Hollenberg brought up the point of seminiferous tubular damage after use of hormones and added that there was increasing feeling that testes which descended after gonadotrophin therapy would probably have descended without any treatment.

The consensus of the panel was that nothing should be done until the immediate pre-puberty period. At that time operation would be the treatment of choice, without the use of gonadotrophic hormones.

A 3-month-old infant with typical cretinoid findings and a protein-bound iodine value of 0.8 gamma per 100 ml. was the third case.

The clinical and laboratory findings of cretinism were described in detail, and a brief discussion of the differences between congenital and acquired cases was presented by Dr. Ducharme. From the metabolic point of view, the various sites in the biosynthetic pathway in iodine metabolism where a block could occur with resulting hypothyroidism were briefly outlined.

The problem of delayed adolescence with presumed growth retardation was discussed by Dr. Hollenberg. He felt that, provided a simple general physical examination together with a few of the more easily performed endocrine tests, such as P.B.I. determination and a skull radiograph to exclude hypothyroidism and pituitary enlargement respectively, were within normal limits, then at least one to two years should elapse before embarking on a complicated endocrine analysis. He felt strongly that the great majority of cases of delayed adolescence prove to be physiological. Dr. Rose asked about the efficacy of the simple thyroid function tests such as the basal metabolic rate test. Dr. Hollenberg replied that, particularly in young infants, the B.M.R. was very unreliable and even in young adolescents could be affected by so many factors that the P.B.I., particularly with the ease of taking a blood sample, is being performed by many centres across Canada, and should be the test of first choice.

Dr. Ducharme mentioned that in one particular type of block in the metabolic pathway, the P.B.I. would be normal, and advised treating the young infant with suspected cretinism by a clinical trial of thyroid extract.

A fourth case had a history of having noted enlargement of the thyroid gland at the age of 12, without symptoms. At the age of 28, the patient, after what was apparently a common cold, developed pain and tenderness in the gland, and on examination a nodule and enlargement of the gland greater than had been apparent on previous examinations were noted. On investigation, the I^{131} uptake was 12% and the P.B.I. value 6.2.

Treatment was begun with L-thyroxin, 0.1 mg. a day, with resultant suppression of all symptoms and reduction in size of the gland. At a return visit several months later, there had been no recurrence of symptoms and no enlargement of the gland was found.

Thyroiditis was classified as (a) common and (b) uncommon. The (a) group included the subacute (self-limited) form and Hashimoto's thyroiditis; the (b) group included Riedel's thyroiditis and suppurative thyroiditis.

Etiology was described under three headings: (1) hormonal (thyrotrophin, by inhibiting thyroid stimulating hormone, relieves the symptoms and reduces goitre size); (2) infectious—(a) viral, possible cause of subacute variety, and (b), bacterial; and (3) autoimmune.

Dr. Hollenberg then briefly outlined a suggested mechanism of the autoimmune variety. He felt that in these cases there was leakage of thyroglobulin from the gland with resultant antibody production causing an antigen-antibody reaction in the thyroid with a greater release of thyroglobulin and resultant greater antibody production.

In Hashimoto's thyroiditis thyroglobulin antibody is present in 80% of cases and the titre is high; in myxedema in 70% of cases and the titre is moderate; in subacute thyroiditis in 50% of cases and the titre is low and transient; in hyperthryoidism in 50% of cases and the titre is low; in non-toxic goitre in 30% of cases and the titre is low; in thyroid cancer in 30% of cases and the titre is low; and when there is no thyroid disease, in 3% of cases and the titre is low.

Despite the gathering of more and more information, the positive role of antibodies still remains to be proved in the etiology of thyroiditis.

Dr. Rose asked which type of thyroid medication to use. Dr. Hollenberg replied that he had no strong feelings on this point and still used desiccated thyroid in the average case.

The final point raised by the panel was that mild thyroiditis is often missed, particularly in children.

The last case was that of an adult with the following history. In 1952, at age 42, the diagnosis of acute diabetes mellitus was made, and he was treated and controlled with PZI, 20 units per day. In 1958, because of extremely good control, which he had exhibited over a long period of time with reduction of his insulin dosage, insulin was finally discontinued and he was carried on diet alone.

He did well until July 1959, when he developed cellulitis, and was put back on insulin with subsequent clearing of his infection. He was finally discharged on lente insulin, 20 units per day. On August 31, 1959, the patient developed a severe acute urticaria which was treated at home, but by September 9 he was deeply in coma with a blood sugar of 852 mg. % and a CO_2 combining power of 2 mEq./l. Enormous doses of insulin were required to treat this coma, but, by the next day, September 10, after administration of 10,000 units of crystalline insulin his blood sugar was 155 mg. %, there was no evidence of continued ketosis and he was easily maintained on 20 units of lente insulin per day. By September 20, he was discharged on the same dose and by May 1960, again because of his well-controlled state, insulin was finally discontinued. By February 1961, that is, after a year without insulin, his blood sugar was 131 mg. % and he had no complaints and felt very well.

The panel felt that this was a case of insulin sensitivity with resultant antibody formation binding both endogenous and exogenous insulin to a very marked degree. It was pointed out that even normal individuals have serum antagonists associated with the plasma albumin fraction and that in patients with diabetic ketosis the marked insulin antagonism is associated with the alpha[1] globulins and disappears when the ketosis is treated. Cases of chronic insulin resistance exhibit the antagonist in the gamma globulin fraction and, therefore, it is presumably an antibody.

Dr. Rose asked why, in these insulin-resistant patients, good results were obtained with the oral preparations. Dr. Hollenberg explained that the resistance and antibodies developed by these patients were to the beef insulin, but as the oral agents stimulate endogenous insulin production and as there are no truly significant antibodies against this in the patient's serum, they did well with the smaller doses of the oral medication.

The following questions were asked from the floor. What problems would arise in the newborn child whose mother had had to be treated during pregnancy with antithyroid drugs? Dr. Ducharme answered that only small doses should be used and no attempt should be made to bring the mother's P.B.I. value down to normal levels because of the dangers of depressing the unborn infant's thyroid. If such treatment has been carried out, the infant may be born with an enlarged thyroid and, if already exhibiting signs of mild hyperthyroidism, may go into thyroid crisis at a few weeks of age. If, however, there is no evidence of hyperthyroidism, then the infant should be treated with thyroid extract, or if respiratory distress is present, owing to the size of the thyroid gland, then the isthmus of the gland should be resected.

The corollary to this question was asked from the floor, that is, what does thyroid extract do in the hyperthyroid pregnant mother? This was answered by Dr. Hollenberg, who said that if the mother was treated to the euthyroid levels this would have no effect on the fetus.

The last question concerned the place of steroids in the treatment of subacute thyroiditis. Dr. Hollenberg answered that the treatment of first choice is thyroid medication and that only if this is unsuccessful should steroids be used, followed finally and only if necessary by radiation.

T. A. BROWN

"THE ACUTE ABDOMEN"

Chairman: *Dr. A. D. McKenzie*, Vancouver
Panelists: *Dr. L. Morisette*, Montreal
Dr. J. G. Howlett, Montreal
Dr. R. A. H. Kinch, London
Dr. J. R. F. Mills, Toronto

A brief introduction was given by the chairman, DR. A. D. MCKENZIE, Head, Department of Surgery, University of British Columbia. Following this, Dr. L. Morisette, Associate Professor of Medicine, University of Montreal, discussed local medical conditions simulating the acute surgical abdomen. Among these he enumerated diaphragmatic pleurisy, acute myocardial infarction, acute pancreatitis and perisplenitis, biliary dyskinesia, gastric crises of tabes, and herpes zoster of the abdominal wall. He pointed out that in most of these situations a careful history and physical examination followed by appropriate laboratory examinations usually results in the correct diagnosis being made. However, he made special note of the problem of abdominal migraine, in which situation the physician has little to go on, and which so often results in futile exploratory laparotomy. He pointed out that psychiatric evaluation is sometimes of benefit in eliminating the diagnosis of migraine equivalents. The chairman then asked Dr. J. G. Howlett, Professor of Medicine, McGill University, to discuss the general systemic medical causes simulating the acute abdomen. Dr.

Howlett discussed briefly such diverse conditions as hemolytic crises, porphyria and bleeding into the bowel wall in patients with a hemorrhagic diathesis. Diabetic acidosis, crises of Addison's disease, staphylococcal enteritis, periarteritis nodosa, enteric fever, infectious hepatitis and infectious mononucleosis can all give rise to the picture of an acute surgical abdomen. Poisoning, e.g. with arsenic or poisonous mushrooms, and the effect of drugs such as the ganglion-blocking agents and phenylbutazone were also mentioned briefly. Dr. Howlett alluded to a rare cause of an acute abdomen, namely periodic peritonitis, which is usually found in patients from Asia Minor, and which gives rise to all of the classic signs and symptoms of acute peritoneal inflammation; this is a benign condition which resolves spontaneously without surgery.

Dr. R. A. H. Kinch, Professor of Obstetrics and Gynecology, University of Western Ontario, then discussed some of the gynecological causes of an acute abdomen, and he indicated that these could be classified under three headings, namely blood in the belly, pus in the belly, or torsion of an ovarian cyst. The gynecologist must always consider first an ectopic pregnancy and acute torsion of an ovarian cyst, because these two conditions demand early operation. He made special mention of two benign conditions which do not require exploration: a leaking Graafian follicle and a corpus luteum cyst, neither of which occur in the first 14 days of the menstrual cycle. Acute pelvic inflammatory disease can usually be diagnosed because of its bilateral involvement. The chairman then asked Dr. Howlett to elaborate further on acute porphyria. Dr. Howlett remarked on the infrequency of this condition, but suggested that a history of previous laparotomy with acute upper abdominal pain precipitated by ingestion of a barbiturate gave a very suggestive history; urine that darkened on standing and gave a positive reaction for porphobilinogen with Ehrlich's aldehyde reagent was confirmatory. Dr. Morisette then discussed further the problem of acute myocardial infarction. He noted that such features as electrocardiographic changes, a pericardial friction rub and an elevated serum transaminase level often appeared late, and he cautioned the audience to be aware of the coexistence of acute myocardial infarction in the presence of a true acute surgical abdomen. He felt that the strongest safeguards against mistaking this diagnosis were by maintaining an awareness of the possibility of its presence and by frequent re-evaluation of the patient during the acute phase.

Dr. J. R. F. Mills, Associate Professor of Surgery, University of Toronto, went on to discuss the roentgenologic examination of these patients. The anteroposterior view of the abdomen with the patient recumbent, right side up, is most helpful in demonstrating free air under the right costal margin in cases of a perforated viscus. In small bowel obstruction the abdominal film shows distended loops of the small bowel with air fluid levels, whereas in large bowel obstruction, one usually sees the distended cecum if the ileo-cecal valve remains competent. Only 10% of biliary calculi are radiopaque, but the demonstration of air in the biliary system, although a rare sign, is pathognomonic of erosion of a stone into the small bowel. Ninety per cent of urinary calculi are radiopaque, and calcification in the area of the pancreas may give a clue in a few cases of pancreatitis. The chest radiograph is helpful in revealing an early pneumonia.

Dr. Kinch went on to discuss the value of posterior colpopuncture and posterior colpotomy in the diagnosis of gynecological causes of an acute abdomen. He advised using a wide bore needle (16G or larger) and placing the patient in the reverse Trendelenburg position for colpopuncture. The withdrawal of pale pinkish fluid suggests a leaking Graafian follicle, whereas dark red blood which does not clot after withdrawal, indicates bleeding into the peritoneal cavity. Posterior colpotomy should not be performed when the uterus is fixed or retroverted as this indicates the presence of adhesions. The incision should be one and a half inches long, and followed by complete abdominal pelvic examination. Dr. Morisette made a few remarks on the special problems of the acute abdomen in the aged patient, where the history is often difficult to obtain and the signs may be less marked. He mentioned dissecting aortic aneurysm as a rare cause in this age group. Dr. Kinch remarked on the special problems in pregnant patients; during the first trimester, the history is often made difficult by the coexistence of nausea and vomiting. In the second trimester, accepted points of tenderness tend to change as a result of displacement of abdominal contents by the gravid uterus, whereas in the third trimester one has difficulty in distinguishing the pain of peritoneal irritation from labour pains.

F. R. P. CRONIN

"PRACTICAL PROBLEMS IN INTRAVENOUS SUPPORTIVE THERAPY"

Chairman: *Dr. Fraser N. Gurd*, Montreal
Panelists: *Dr. J. C. Beck*, Montreal
Dr. R. A. Macbeth, Edmonton
Dr. Eudore Savoie, Montreal

DR. FRASER N. GURD, Professor of Surgery, McGill University, in his introductory remarks laid the ground rules for the discussion by outlining the three practical problems of intravenous therapy: day-to-day maintenance, replacement of dynamic (concurrent) losses, and replacement of fluid deficit. Approximately 2000 c.c. of water is required daily to cover insensible water loss, water loss in the urine, and abnormal losses, such as are associated with fever, sweating and the accumulation of fluids in the so-called "third space" i.e. pleural or peritoneal space and the tissue edema of burns.

Dr. Gurd mentioned that 80 mEq. each of sodium and potassium ion represent average daily requirements, whereas 100 g. of carbohydrate are required for nourishment and maximal protein-sparing effect. Dynamic losses should be made up with solutions which, as nearly as possible, approximate that of the actual fluid lost. The ionic constituents of the plasma and the various intestinal juices were discussed, and it was pointed out that, whereas the sodium content of most gastrointestinal losses approaches that of plasma, the potassium content is four to six times higher.

Dr. R. A. Macbeth, Professor and Head, Department of Surgery, University of Alberta, went on to discuss the problem of repairing static deficits and he listed the four questions that every physician or surgeon charged with this problem should ask himself: (1) Is there any fluid deficit? (2) Is there any sodium or chloride deficit? (3) Is there any acid-base abnormality?

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(4) Is there any other cation deficit? The answer to the first question is to be found largely in the historical assessment of the patient: in the duration of the illness, the extent of the fluid restriction and the extent of the abnormal loss. Up to 2% of the body fluids may be lost without obvious signs or symptoms, a 2-4% loss gives rise to central nervous system depression, 4-6% to peripheral vascular collapse, and when 10% is lost the patient becomes comatose. Burns, paralytic ileus and diarrhea give rise predominantly to isotonic dehydration, pyloric stenosis with vomiting is the commonest cause of chloride loss and small bowel fistula the commonest cause of sodium loss. In metabolic alkalosis there is evidence of acid loss with signs of tetany and a rise in CO_2 combining power, whereas in metabolic acidosis there is a history of loss of base ion, often with Kussmaul respirations and a lowering of the CO_2 combining power. In discussing therapy Dr. Macbeth recommended paying attention first of all to correction of acid-base imbalance, which in itself often initiates correction of the fluid deficit. For metabolic alkalosis he recommended the use of normal saline rather than ammonium chloride solution, provided renal function is satisfactory. For metabolic acidosis he recommended the use of 1/6 molar lactate solution, although he pointed out that stable preparations of sodium bicarbonate solution are now available. Where replacements of over 2000 c.c. were required, he recommended the use of solutions whose ionic constituents more closely approximated that of the plasma. Although formulae and rules are available for the correction of static deficits, Dr. Macbeth felt that slavish adherence to rigid formulae should be rejected in favour of frequent clinical evaluation of the patient's status.

Dr. E. Savoie continued the discussion by outlining the cause and treatment of acute renal failure in relation to shock. Dr. Savoie pointed out that, when the clinician is faced with the problem of acute reduction or suppression of urine, the differentiation of renal from prerenal and postrenal causes is most important. The hallmarks of renal failure are a falling urine output with a rising blood urea nitrogen level despite adequate fluid replacement. Urinary output averages between 100 and 300 c.c. per day, the urine specific gravity being about 1.010 to 1.012. There is albumin in the urine, and often red blood cells and casts in the urinary sediment. In prerenal failure the specific gravity of the urine is higher and the output is generally 400 c.c. or greater. In doubtful cases the trial administration of 500 c.c. of glucose and water will cause an increased urinary output in cases of prerenal azotemia. The pathogenesis of acute renal failure is still obscure, but decreased renal blood flow and the action of nephrotoxic agents, either alone or in combination with renal ischemia, are thought to be the etiological agents in the majority of cases. Dr. Savoie stated that the best therapy for this condition was prophylactic therapy, and he listed adequate preoperative correction of fluid and electrolyte deficits with replacement of blood, plasma and body fluids as being preventive in most instances. He alluded to the recent introduction of infusions of mannitol and dextran to maintain renal blood flow in patients with severe burns. In the management of acute renal failure, overhydration is the greatest danger during the oliguric phase. Fluid intake should be limited to approximately 500 c.c. and given in the form of 20%-50% glucose in order to obtain the maximum protein-sparing action. Alarming rises in serum potassium, which are prone to occur following crush injuries, should be treated with hypertonic glucose and insulin, and the oral administration of cation exchange resins. During the diuretic phase, on the other hand, excessive potassium loss must be carefully watched for and corrected.

Dr. J. C. Beck, Associate Professor of Medicine, McGill University, finished up the session by discussing what he called some of the medical weak spots in intravenous fluid therapy of certain groups. Prominent among these were individuals in the older age group who are particularly prone to develop water depletion. He stated that many do not have an intact thirst mechanism and that others may have loss of urinary concentrating power. This latter factor may be exaggerated by the administration of a heavy solute load (tube feedings, diabetes). In addition, many elderly people are unusually susceptible to sodium loss, showing signs of hyponatremia with deficits of the order of 200-300 mEq. In water intoxication, which is nearly always the result of overenthusiastic intravenous fluid therapy, the signs are those of hyponatremia with a normal fluid volume. Fingerprint edema of the skin is a valuable sign in this condition; the therapy is water restriction, and occasionally there may be a place for the cautious administration of hypertonic saline solution and corticosteroids. Dr. Beck alluded to a rare condition found in elderly people known as asymptomatic hyponatremia. Patients with this condition show a chronically reduced level of serum sodium; no treatment is required. Congestive failure may result from overzealous attempts to correct this apparent biochemical abnormality. The second medical weak spot which Dr. Beck discussed was in the treatment of patients who have been on prolonged corticosteroid therapy. These patients have a hypokalemic hypochloremic alkalosis which is intensified by surgery and injudicious sodium chloride infusion. The therapy of this situation lies in providing intravenous potassium supplements. Iatrogenic adrenal insufficiency can be provoked by abrupt cessation of long-term steroid therapy or by increased demand associated with the stress of illness and surgery. The last group of patients Dr. Beck mentioned were those who are treated by the newer and more potent oral diuretics, namely the thiazide derivatives and the spiraloctones. These patients all tended to be depleted of potassium. Dr. Beck felt that these agents should never be administered without a potassium supplement, particularly in patients who were following a low salt diet.

F. R. P. CRONIN

"PRENATAL CARE"

Chairman: *Dr. B. D. Best*, Winnipeg
Panelists: *Dr. F. J. Tweedie*, Montreal
Dr. O. A. Schmidt, Winnipeg
Dr. P. A. Rechnitzer, London
Dr. W. R. Foote, Montreal

Following the chairman's introductory remarks, DR. P. A. RECHNITZER discussed the management of patients with arterial hypertension during pregnancy. He noted that the fetal salvage rate was better when hypertensives were induced two weeks before term, or were brought in for one week of bed-rest before term. Dr.

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Statement on medical services insurance

By direction of the General Council at the 94th Annual Meeting the Statement on Medical Services Insurance is reprinted herewith for the information of the members. Elaborated in June 1960 after extended debate and with due consideration of all the ideas expressed, the Statement constitutes the current policy of the Canadian Medical Association on a matter of importance to the medical profession and to the people of Canada. It is suggested that this page be removed and that the Statement be retained for ready reference.

The Canadian Medical Association believes that:

- The highest standard of medical services should be available to every resident of Canada.
- Insurance to prepay the costs of medical services should be available to all regardless of age, state of health or financial status.
- Certain individuals require assistance to pay medical services insurance costs.
- The efforts of organized medicine, governments and all other interested bodies should be coordinated towards these ends.
- While there are certain aspects of medical services in which tax-supported programs are necessary, a tax-supported comprehensive program, compulsory for all, is neither necessary nor desirable.

(OVER)

The Canadian Medical Association will support any program of medical services which adheres to the following principles:

1. That all persons rendering services are legally qualified physicians and surgeons.
2. That every resident of Canada is free to select his doctor and that each doctor is free to choose his patients.
3. That the competence and ability of any doctor is determined only by professional self-government.
4. That within his competence, each physician has the privilege to treat his patients in and out of hospital.
5. That each individual physician is free to select the type and location of his practice.
6. That each patient has the right to have all information pertaining to his medical condition kept confidential except where the public interest is paramount.
7. That the duty of the physician to his individual patient takes precedence over his obligations to any medical services insurance programs.
8. That every resident of Canada, whether a recipient or provider of services, has the right of recourse to the courts in all disputes.
9. That medical services insurance programs do not in any way preclude the private practice of medicine.
10. That medical research, undergraduate and postgraduate teaching are not inhibited by any medical services insurance program.
11. That the administration and finances of medical services insurance programs are completely separate from other programs, and that any board, commission or agency set up to administer any medical services insurance program has fiscal authority and autonomy.
12. That the composite opinion of the appropriate body of the medical profession is considered and the medical profession adequately represented on any board, commission or agency set up to plan, to establish policy or to direct administration for any medical services insurance program.
13. That members of the medical profession, as the providers of medical services, have the right to determine the method of their remuneration.
14. That the amount of remuneration is a matter for negotiation between the physician and his patient, or those acting on their behalf; and that all medical services programs make provision for periodic or automatic changes in remuneration to reflect changes in economic conditions.

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F. J. Tweedie of the Department of Obstetrics, Royal Victoria Hospital, Montreal, was then called upon to discuss the problem of bleeding during the first trimester. He pointed out that in nearly every case this resolved itself into the differential diagnosis between spontaneous abortion and inconsequential bleeding of the first trimester. In 60%-70% of cases of spontaneous abortion the etiological factor lay in a blighted ovum. In the remaining cases one had to consider hormonal imbalance, congenital malformation of the uterus, nutritional deficiency and psychic factors. In treating the patient with threatened abortion, restriction of physical activity was the most important single factor. Hormonal treatment with progesterone plus estrogen therapy was advised where a hormonal imbalance was suspected, particularly in the habitual aborter, which he defined as a patient with a history of three successive miscarriages. He also advised hormone therapy in patients who were fertility problems and in those in whom there was a history of an irregular menstrual cycle.

Dr. O. A. Schmidt, Assistant Professor of Obstetrics and Gynecology, University of Manitoba, went on to discuss viral disease as an indication for therapeutic abortion. He pointed out that an association had been drawn between maternal rubella during the first trimester and deafness, cataracts, congenital cardiac malformation, microcephaly and mental retardation in the offspring. He felt, however, that there was no place for therapeutic abortion after the first twelve weeks of pregnancy.

Dr. W. R. Foote, Assistant Professor of Obstetrics and Gynecology, McGill University, then took up the problem of bleeding in the last trimester, and he noted that painless bleeding in the last trimester should occasion a diagnosis of placenta previa until proven otherwise. The hospital is the only place to treat a patient with this complication. He had not found soft tissue roentgenography useful in establishing the site of implantation of the placenta. He advised carrying the baby to the 37th week of gestation, and arranging for examination in the delivery room, with the delivery room staff prepared to assist at either a vaginal or abdominal delivery. If central or lateral placenta previa is revealed at examination, then Cesarean section should be performed without delay. Speculum examination of the cervix should not be omitted, because a polyp or cervical erosion can be a rare cause of bleeding in this situation. It should not be forgotten, however, that occasionally both polyp and placenta previa co-exist. Retroplacental hemorrhage demanded whole blood replacement; fresh blood should be used if available to prevent the possibility of the development of hypofibrinogenemia. Induction of labour with intravenous Pitocin should be started, and if after six hours the patient is not in hard labour, Cesarean section should be performed. If at section, the uterus is found to be damaged by extravasated blood, a Porro section should be performed.

Dr. B. D. Best, Professor of Obstetrics and Gynecology, University of Manitoba, continued the discussion by outlining the usefulness of placentography, which he felt, in the hands of a skilled radiologist, permitted the confident diagnosis of a highly situated placenta, and allowed the obstetrician to discharge a certain number of patients showing last trimester bleeding, thus saving them needless hospitalization. He also stressed the serious consequences of abruptio placentae, namely hypofibrinogenemia, fetal loss and renal shutdown, each of which are enhanced by delay in instituting appropriate therapy.

Dr. Tweedie wound up the session by discussing the syndrome of the incompetent cervix, which he felt was the commonest cause of abortion in the middle trimester. In this situation the internal os appears to relax, either owing to a functional disturbance or to previous trauma, and after minimal cramps the waters break and the uterine contents are rapidly expelled. In this situation he favoured a suture of the internal os, which in selected cases he felt resulted in a 70%-80% fetal salvage rate, the suture being cut during subsequent labour at term.

F. R. P. CRONIN

"HYPERTENSION — ATHEROSCLEROSIS"

Chairman: *Dr. Jacques Genest*, Montreal
Panelists: *Dr. Louis Horlick*, Saskatoon
Dr. J. A. Lewis, London
Dr. W. F. Connell, Kingston
Dr. J. D. Morrow, Toronto
Dr. A. E. Thomson, Winnipeg

The teaching session on the clinical management of patients with hypertension with and without atherosclerosis was presented in a new and provocative manner. Clinical cases were presented and the management of each specific problem was considered.

The first case presented was a woman of 35 years, with a blood pressure of 170/105 mm. Hg, a tense and anxious person whose blood pressure fell to normal levels with rest or peace of mind. She showed no physical signs of damage due to her disease. Dr. A. E. Thomson, Assistant Professor of Medicine, University of Manitoba, considered that the immediate problems here were small, that no medical therapy other than that designed to solve her emotional problems was indicated, but that one should follow up this patient, since her ultimate prognosis was not known.

The second case was a 45-year-old male, with a blood pressure of 200/125 mm. Hg. He had hemorrhages and exudates in his fundi, and evidence of left ventricular hypertrophy and strain on his electrocardiogram. Renal function was adequate. Dr. J. D. Morrow felt that this was a case of severe essential hypertension, one which could be salvaged completely by adequate therapy, since renal function was normal. The object of therapy in this kind of a case is perfect control of the blood pressure. More damage would ensue if the blood pressure was allowed to remain elevated. Drug therapy should be begun with a Rauwolfia preparation and chlorothiazide, as a background to prepare the patient for the use of more potent drugs. Dr. Morrow stated that he would then add guanethidine, an agent which selectively blocks sympathetic activity. If diarrhea or postural hypotension became severe, the dose of guanethidine would be reduced and a ganglionic blocking agent would be added; or, if this was ineffective, hydralazine would be used. The panel were all agreed that bretyllium tosylate can no longer be considered a clinically useful drug. Dr. J. Genest, Physician and Director, Department of Clinical Medical Research, Hôtel-Dieu de Montréal, and Associate Professor of Medicine, University of Montreal, stated that if the blood pressure were reduced below 170/110 mm. Hg, the incidence

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of cardiovascular accidents would decrease greatly. If the diastolic pressure is brought as low as 80-95 mm. Hg, then control is excellent.

A 50-year-old man, restless and confused, with a blood pressure of 280/170 mm. Hg, complaining of severe headache and blurring of vision, a case of hypertensive encephalopathy, was then discussed. Dr. J. A. Lewis, Assistant Professor of Medicine, University of Western Ontario, pointed out that treatment of this medical emergency is guided by the principle that potent agents without hazard are needed at this time. Both parenteral reserpine and parenteral veratrum will control this condition rapidly and safely. At the present time he is using pempidine by mouth for these patients and finds that it is also safe and effective therapy. Once the blood pressure is brought under control, combined drug therapy should be instituted.

Dr. W. F. Connell, Professor of Medicine, Queen's University, discussed a 55-year-old man with hypertension and angina pectoris. If the angina pectoris was of long duration and easily avoided, he would treat only the hypertension. If the angina was severe and of recent onset, he would institute anticoagulant therapy as well. Dr. L. Horlick, Professor of Medicine, University of Saskatchewan, pointed out that the angina will generally improve as the diastolic pressure decreases.

Dr. Morrow discussed the case of a 42-year-old man with hypertension and congestive heart failure. He pointed out that this man's heart was unable to tolerate both the normal work load and an elevated peripheral resistance. He advocated treating the congestive heart failure by digitalis and diuretics, and lowering the blood pressure to decrease the cardiac work load.

A 60-year-old man with hypertension and with recurring episodes of right-sided weakness and dysarthria was discussed by Dr. Horlick. The first step in management of this patient was to examine the patient and determine whether the occlusion responsible for his episodes of cerebral arterial insufficiency was extracranial and amenable to surgery. Then, if surgery is to be performed, angiography may be carried out, preferably via a brachial or femoral arterial catheter. The blood pressure may be lowered slowly, but new thrombosis is a hazard. Anticoagulants may be used, but there is an added risk of intracerebral hemorrhage in the presence of hypertension.

Dr. Lewis discussed an anemic, uremic 20-year-old woman with papilledema and retinopathy. Therapy in cases such as this often leads to no useful improvement, but he felt that efforts should be directed to lowering the blood pressure slowly and to raising the hemoglobin level towards normal. Progressive renal failure and even complete anuria are the chief hazards of hypotensive therapy.

In striking contrast, a 60-year-old woman with a blood pressure of 250/100, with visible and tortuous brachial arteries, and a dilated calcified aorta has, according to Dr. Connell, systolic hypertension due to rigid arteries and her prognosis without therapy is often surprisingly good.

In conclusion, Dr. Genest pointed out that 85-90% of patients with essential hypertension may be controlled with medication. The choice of agents and aims of therapy were outlined.

C. A. GORESKY

SECTION OF GASTROENTEROLOGY

"THE DIAGNOSIS AND MANAGEMENT OF HIATUS HERNIA AND ESOPHAGITIS"

Chairman: *Dr. R. C. Dickson*, Halifax
Panelists: *Dr. R. G. Fraser*, Montreal
Dr. D. D. Munro, Montreal
Dr. C. M. Ballem, Montreal

DR. R. C. DICKSON, Physician-in-Chief, Victoria General Hospital, Halifax, and Professor of Medicine, Dalhousie University, in his introductory remarks, pointed out that esophagitis is the commonest disorder of the upper gastrointestinal tract. Increased intra-abdominal pressure prolonged over a sufficient period of time will cause reflux and ensuing esophagitis, as exemplified by the lumber workers in Nova Scotia during the great depression when they had to work very hard in a bent position sawing or piling logs. Many of these men developed esophagitis, called by them "fiery gullet". The mechanism which opposes the occurrence of reflux can give in rather easily.

The first part of the panel discussion consisted of a description of the normal anatomy, physiology and radiology of the esophagogastric junction region. It was pointed out by Dr. D. D. Munro, Assistant Surgeon, Royal Victoria Hospital, Montreal, that hiatal hernias do not differ from other hernias. The esophagogastric junction should lie below the hiatus, and if it is much above it, normal competence sooner or later is lost. He spoke of the importance of the anchoring effect of the phreno-esophageal ligament and, most of all, the importance of diaphragmatic crura which are a split bundle of the right diaphragm. Their major task is to angulate the esophagogastric border, thereby preventing reflux from occurring.

Dr. R. G. Fraser, Assistant Professor of Radiology, McGill University, described the radiology of this region. He emphasized that though the existence of an anatomical lower esophageal sphincter is a matter of considerable debate among anatomists, a functional sphincter can be seen on radiographs approximately 2-3 cm. above the hiatus. Right below it, there is the esophagogastric vestibule which can be confused with a hiatus hernia. He proved by cineradiography that the crura angulating the esophagogastric junction come really from the right diaphragm and not the left, as left phrenic paralysis increases the angulation whereas right phrenic paralysis causes the angulation to disappear.

Dr. C. M. Ballem, Royal Victoria Hospital, Montreal, pointed out that in esophageal motility studies with pressure transducers the physiological sphincter can be demonstrated causing a so-called high pressure area, usually immediately above the hiatus. When the physiological sphincter does not function properly, the so-called high pressure area does not occur on the tracing. He cited Woodward who claims that there is a rather wide area extending from the lowermost part of the esophagus to the cardia, where the mucosa is made up of so-called "junctional epithelium" consisting of tall columnar cells and no specific gastric mucosa cells. This would explain the fact that esophagitis occurs only in the presence of reflux.

Dr. Munro, giving the classification of hiatus hernia, added that congenital shortening of the esophagus is rarely seen in adult practice. Most of the time one sees an acquired shortening associated with the sliding type of hernia, which is the most frequent type en-

countered. Here the esophagogastric angle is lost. The other type is the paraesophageal hernia or "roller" where the junctional angle is usually preserved lying below the hiatus. This prevents the occurrence of reflux. In this case the complaints of the patient, instead of pyrosis, are distension and a feeling of pressure in the chest. Quite often, however, there is a mixed type present.

In demonstrating cineradiographic films of different types of hiatus hernias, Dr. Fraser pointed out that the most important single method of diagnosis is to have the patient bending over touching his toes. In this position the sliding hernias can be demonstrated much more accurately than in the Trendelenberg position.

Dr. Ballem emphasized the problem of diagnosis of esophagitis. The physiological sphincter can be present or might be lost. Radiographs reveal only the advanced stage of esophagitis, mainly the consequences of fibrosis. Therefore, esophagoscopy is a very important aid in diagnosis. He found that signs of esophagitis can be present sometimes despite a normal-looking mucosa. In these cases, biopsy is well worth while, as inflammation sometimes can be demonstrated only in the submucosa.

The importance of the physiological esophageal sphincter was stressed by Dr. Dickson who stated that he had seen many cases where, in the presence of well-developed hiatus hernia (even the sliding type), reflux and esophagitis would not occur, since the sphincter functioned properly.

The operative failures were attributed by Dr. Munro to failures of surgical technique as the restoration of the esophagogastric angle is a rather difficult procedure, and reduction of the hiatus hernia will not suffice.

Because of a lack of time, medical treatment and the problem of selection of patients for operation were not discussed.

J. SOLYMAR

"EVALUATION OF CURRENT DIAGNOSTIC METHODS IN DISEASES OF THE DIGESTIVE TRACT"

Chairman: *Dr. A. Bogoch,* Vancouver
Panelists: *Dr. A. Jutras,* Montreal
Dr. J. Sidorov, Halifax
Dr. P. Letendre, Montreal
Dr. J. M. Finlay, Toronto
Dr. D. J. Buchan, Saskatoon
Dr. P. M. O'Sullivan, Toronto

Following the panel discussion on the diagnosis and management of hiatus hernia and esophagitis, six individual papers were given on current diagnostic methods in diseases of the digestive tract.

"Evaluation of Teleroentgen Studies of the Digestive Tract"

DR. A. JUTRAS, Professor and Director, Department of Radiology, University of Montreal, gave an evaluation of teleroentgenography in the examination of the digestive tract. The machine is remotely controlled. The picture is seen on an image amplifier, and films are taken with cineradiography. With this technique the examiner is completely protected. On the cineradiogram more details can be seen than on conventional films, and the dynamics of the studied organs can be followed as well. At the same time the price of these films is less than the price of films taken with a conventional x-ray machine, and their storage is much easier.

"Esophageal Acid Perfusion Test and Mortality Studies"

DR. J. SIDOROV of Halifax presented evidence that the esophageal acid perfusion test is a reliable aid in the diagnosis of esophagitis. This test consists of perfusion of a solution of 0.1 HCl through an esophageal tube placed at the level of the mid-esophagus. This test is considered to be positive if the acid perfusion reproduces the patient's original symptoms (pain, heartburn, etc.) and if these symptoms can be relieved by subsequent perfusion of an antacid. Saline perfusion at the same time should have no effect on eliciting the patient's original complaints. Esophageal motility studies can also be very helpful in demonstrating the presence or absence of a physiological esophageal sphincter. The relation of this sphincter to the hiatus is of help in the diagnosis of hiatus hernia. The esophageal peristalsis can be studied as well, which would be interfered with in severe esophagitis, scleroderma, cardiospasm, etc.

"Esophagoscopy and Gastroscopy"

DR. PAUL LETENDRE, Chief of Medicine, Hôtel-Dieu, and Professor of Clinical Medicine, University of Montreal, presented his experience with esophagoscopy and gastroscopy, and showed that these procedures are valuable in elucidating certain obscure cases with involvement of the upper gastrointestinal tract.

"Tests of Intestinal Absorption"

DR. JOHN FINLAY of Toronto presented his experience with three tests used in diagnosing intestinal malabsorption and so-called protein-losing gastroenteropathy. He found the xylose tolerance test to be very valuable in cases where the intestinal absorption is disturbed. As far as steatorrhea is concerned, he found the chemical fat analysis of the stool to be the only reliable method for demonstrating steatorrhea. In his hands the radioactive I^{131}-triolein method for fat absorption study proved inadequate, as too many false-positive and false-negative results were obtained. Radioactive PVP study for the demonstration of leakage of protein into the bowel is a new technique, and its place and reliability have not been definitely established.

"The Value of Peroral Small Bowel Biopsy"

DR. D. J. BUCHAN, Assistant Professor of Medicine, University of Saskatchewan, found the peroral small bowel biopsy to be of value in certain cases of malabsorption, mainly those with adult celiac disease.

"Liver Biopsy Using the Menghine Needle"

DR. PAUL O'SULLIVAN of Toronto reported on his experience with liver biopsy using the Menghine needle. He found the liver biopsy to be a very safe procedure with this needle. There were no complications in more than 80 cases of liver biopsy, and the pathology specimens were much more suitable for proper histological evaluation than the specimens taken by other methods.

J. SOLYMAR

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Wednesday, June 21

"THE VALUE OF ANTICOAGULANT THERAPY"

Chairman: *Dr. K. J. R. Wightman*, Toronto
Panelists: *Dr. Paul David*, Montreal
Dr. H. J. M. Barnett, Toronto
Dr. Louis Horlick, Saskatoon

DR. K. J. R. WIGHTMAN, Professor of Medicine, University of Toronto, and Physician-in-Chief, Toronto General Hospital, introduced the session by stating that anticoagulant therapy is designed to prevent abnormal clotting in the channels of the body through which blood flows. It is applied when thrombosis has occurred or is anticipated. The clinical criteria for diagnosing thrombosis include local symptoms of obstruction of the vessel, symptoms arising distal to the obstruction, pain, infarction of the area involved, and even sudden death. Since the natural history of the process is so variable, he emphasized that large series of cases are needed to provide clear-cut demonstrations of benefit from this therapy. He emphasized that the therapy must be controlled by utilizing reliable laboratory methods or increasing risk of hemorrhage may occur.

The physiology of hemostasis was dealt with by Dr. L. Horlick, Professor of Medicine, University of Saskatchewan. He dealt with, firstly, the vascular factor in hemostasis, changes in the endothelial surface may lead to clotting thereon. Secondly, the platelet factor in clotting was considered. Minute vascular injuries are sealed off by a hemostatic plug of platelets, which later undergoes viscous metamorphosis, so that these clump and fuse together. Later, fibrin aggregates over this plug. The third part, clotting of the blood itself, was classified into two parts, an intrinsic and an extrinsic system. The intrinsic system, composed of platelets, antihemophilic globulin, plasma thromboplastin component (factor IX), plasma thromboplastin antecedent and Hageman factor, react to form a hypothetical substance which reacts with factor V, Stuart factor (factor X), and calcium ion to provide thromboplastic activity which promotes the conversion of prothrombin to thrombin, this in turn resulting in fibrin formation from fibrinogen. This is a slow-acting system which plugs leaks *in vivo*. The extrinsic system, a tissue factor + factor VII similarly react after tissue injury with factor V, Stuart factor and calcium ion, to provide thromboplastic activity, but much more rapidly. Dr. Horlick felt that there probably is a constantly shifting flux of procoagulant and anticoagulant factors, and the problem still to be solved is the identification of the factor which upsets the balance so that thrombosis occurs *in vivo*.

The actions of anticoagulant drugs of two varieties, coumarin and indanedione, were considered. Coumarin administration leads to a fall in factor VII, then in prothrombin, and later in factors IX and X. On cessation of therapy, factor VII recovers most quickly, and IX most slowly. Indanedione administration results in a depression of the same factors, but IX and X recover even more slowly on cessation of indanedione therapy than on cessation of coumarin derivatives. Vitamin K_1 oxide causes levels of factors VII and prothrombin to rise quickly, IX and X more slowly. Prothrombin time may return to normal, whereas, for a period, other clotting factors may still be 10-50% of normal. The coumarin derivatives have a slower onset of action than the indanedione group.

Anticoagulant therapy must be regulated by laboratory measurement of the clotting properties of blood. Usually the prothrombin time is measured. The selectivity of this test will vary somewhat with the source of thromboplastin, but the test as it is used is mostly sensitive to prothrombin rather than to other factors of the intrinsic system. The prothrombin time should be at least twice the normal value during therapy. Long-term anticoagulant therapy is fraught with hazard whenever no good method of laboratory control is available, or wherever the patient is unco-operative or unreliable.

The application of anticoagulant therapy in two fields, neurology and cardiology, was then considered. Dr. H. J. M. Barnett, Associate in Medicine, University of Toronto, considered the use of anticoagulant drugs in neurological problems. Most of the knowledge accumulated relates to diseases of the larger vessels, the carotid and basilar arteries. This has arisen since angiography has shown that repeated small strokes are not the result of repeated small emboli or of thrombosis in small vessels, but that these are often due to lesions in the larger vessels. Subsequent clinical investigation has shown that many patients have warning episodes prior to major calamities. Of 87 cases proved by angiography, two-thirds of the patients presented with transient ischemic attacks, attacks in which some part in the distribution of a large vessel ceased to function for an hour or two. The cause ranged from an epileptogenic focus of damage, carotid sinus hypersensitivity, hemorrhage into an atheromatous plaque, orthostatic hypotension, and variations in cardiac output, to an anticoagulant responsive group. He quoted a case report by Dr. Miller Fisher in which recurrently a visible whitish cloud appeared in a retinal arteriole, accompanying subjective complaints of blindness. The visible lesion would regress, and so would the subjective symptoms. The phenomenon ceased when anticoagulant therapy was begun. He felt that perhaps a similar phenomenon occurred in cerebral arterioles during many transient ischemic episodes, and that anticoagulant therapy would stop this phenomenon.

Anticoagulant therapy in cerebrovascular disease was considered separately in patients with established cerebral infarction, in patients with transient ischemic episodes, and in patients with strokes in evolution. Marshall has shown that where established cerebral infarction is present, no help is given to the patient, and that harmful hemorrhage may even result. Fisher has shown that where episodic but increasing damage is occurring (i.e. strokes in evolution), the number of major infarcts which take place may be diminished. Where transient ischemic episodes are occurring, the number of these may be greatly diminished, with attendant decrease in morbidity, by anticoagulant therapy. Such therapy should be used with caution, however, and should be utilized only after adequate diagnostic study has been pursued.

Dr. Paul David, Associate Professor of Medicine, University of Montreal, considered the value of anticoagulant therapy in cardiology. He discussed its application to acute myocardial infarction, to impending myocardial infarction, and to established angina pectoris. The results in impending myocardial infarction are sometimes dramatic, but are difficult to evaluate. Anticoagulant therapy would seem indicated in angina pectoris but would so greatly increase the numbers of patients to be followed up by laboratory tests that

the task would be impossible. Dr. David presented a large series of cases of acute myocardial infarction in which heparin was started immediately, followed by dicoumarol administration. Comparing the untreated group with the treated group, he found that the one significant statistical difference present on follow-up was in mortality. The mortality difference was particularly marked in males under the age of 60. Here anticoagulant therapy does produce definite diminution in mortality. The success of this study and the relative lack of hemorrhagic complications were attributed to the efficient surveillance of the patients by the anticoagulant clinic.

Summarizing, Dr. Wightman pointed out that the indications for anticoagulant therapy are well established in some circumstances, but that the use of this therapy was governed both by the availability and reliability of laboratory tests, and by the co-operation of the patient.

C. A. GORESKY

"THE SIGNIFICANCE OF RECTAL BLEEDING"

Chairman: *Dr. Ian Mackenzie*, Halifax
Panelists: *Dr. R. A. Mustard*, Toronto
Dr. I. T. Beck, Montreal
Dr. C. Biro, Saskatoon
Dr. A. G. Thompson, Montreal

At the outset, the chairman, DR. I. MACKENZIE, Professor of Surgery, Dalhousie University, expressed regret that Drs. Bruneau and Rogers were unable to attend and thanked Dr. A. G. Thompson for joining the panel at such short notice. Dr. I. T. Beck then opened the discussion by outlining the significance of the appearance of the blood from rectal bleeding in relation to the site of origin. He noted that bright red blood, particularly when not mixed well with the stool, generally emanated from the sigmoid colon or below; dark red blood, from the colon or lower ileum; and tarry stool, from the upper gastrointestinal tract. Pure blood was usually of anal origin. He pointed out that these rules were by no means infallible, and that the change in appearance of blood was due to the conversion of hemoglobin to acid hematin. This change occurs in about one hour in acid medium, and much longer in neutral or alkaline media. The appearance of the stool, then, is dependent to a large degree on the degree of intestinal motility.

Dr. C. Biro discussed the special problems of rectal bleeding in children, where physical examination and endoscopy are not as reliable. Constipation and foreign bodies should not be overlooked as causes of mild rectal bleeding. In cases of massive bleeding, intussusception or volvulus was usually the cause in the younger child, whereas ulcerative colitis was commonest in the older age group. The typical current jelly stool was not always present in intussusception, and a tumour could usually be felt in ileocecal and not in ileoileal intussusception. He mentioned that Meckel's diverticulum was the commonest cause of sudden, severe and painless rectal bleeding in patients under the age of two.

In discussing rectal bleeding in adults, Dr. R. A. Mustard, Assistant Profesor of Surgery, University of Toronto, pointed out that internal hemorrhoids were by far the commonest cause of rectal bleeding in adults, but that carcinoma was by far the most important cause and that the incidence of carcinoma increases with age. Intestinal polyps, diverticula, and ulcerative colitis were other common local causes in adults. Of general systemic conditions which cause rectal bleeding, hemorrhagic diathesis, allergies and drugs should not be forgotten.

The chairman asked Dr. Beck to discuss the relationship of the amount of blood in the stool to the amount of bleeding. Dr. Beck pointed out how difficult it was to assess the amount of bleeding in cases of melena and he noted an apparent discrepancy, in that a patient may bleed to the point of profound shock without melena appearing and yet 60 c.c. of ingested blood will produce a tarry stool under certain circumstances. Assessment of bleeding in the early stage is difficult where the hemoglobin and hematocrit values remain unaltered. Pallor, tachycardia and a fall in blood pressure are far more reliable signs. An increase in the pulse rate associated with a feeling of faintness when the patient is placed in the upright position is a valuable sign of early bleeding. All gastrointestinal bleeders should be considered as "massive bleeders" until proved otherwise.

Dr. Mustard took up the problem of pain in relation to bleeding, and pointed out that hemorrhoids, contrary to popular opinion, are a painless condition; neither is pain commonly associated with carcinoma, unless there is associated obstruction or penetration with peritoneal irritation, or unless the carcinoma extends to the abdominal wall. Pain with bleeding can be caused by polyps associated with recurrent temporary bowel obstruction and also with diverticulitis. Dr. Thompson commented on the presence of mucus associated with rectal bleeding and expressed the opinion that larger amounts of mucus were seen in cases of irritable colon than in frank ulcerative colitis.

Points to be remembered in diagnosis of rectal bleeding were summarized by Dr. Mustard. First and foremost, the physician should make sure that the appearance of the stool is in fact due to blood. Once certain, he should then try to determine whether it emanates from above or below the ligament of Treitz. Insertion of a nasogastric tube is helpful in determining this. Dr. Mustard pointed out that 85% of severe bleeding occurs from above the ligament of Treitz. In taking the history, particular attention should be paid to previous gastrointestinal function, a history of operation, results of previous barium examination, a history of familial bleeding tendency, and the use of drugs. On physical examination the stigmata of cirrhosis often gave the clue to bleeding from esophageal varices. As far as radiological examination was concerned he pointed out that the barium enema is an incomplete examination of the large bowel, in that the rectum is not well shown, and should be combined with digital and proctoscopic examination of the rectum. Dr. Beck wound up the panel discussion by outlining the medical management of severe gastrointestinal bleeding. This emergency situation, he felt, should be handled by immediate surgical consultation and by grouping and cross-matching patients without delay for five to ten bottles of whole blood. This amount of blood, he felt, should always be held in reserve. The immediate objectives should be to maintain blood volume and to determine the bleeding source. The team of physician and surgeon should reassess the patient's clinical status, at least every four hours. Indications for surgery, he felt, were an inability to keep up with blood loss after 24 to 48 hours and the recurrence of bleeding within a few days.

F. R. P. CRONIN

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"CHRONIC RESPIRATORY DISEASE,
ITS DIAGNOSIS AND MANAGEMENT"

Chairman: *Dr. R. V. Christie*, Montreal
Panelists: *Dr. D. V. Bates*, Montreal
Dr. J. A. P. Paré, Montreal
Dr. R. G. Fraser, Montreal

At this session, conducted by DR. R. V. CHRISTIE, Professor and Chairman, Department of Medicine, McGill University, and Physician-in-Chief, Royal Victoria Hospital, the clinical history, radiological presentation, pulmonary function tests, and management of a series of patients were discussed.

The first two cases were men presenting with the onset of dyspnea following exposure to industrial gases. The first patient, exposed to chlorine gas, was found to have no demonstrable abnormality in pulmonary function at rest, but hyperventilated on exercise. The diagnosis was respiratory neurosis. The second patient, a 33-year-old man, developed acute pulmonary edema shortly after massive exposure to SO_3. Subsequent to this acute episode he developed dyspnea of such degree that he found it difficult to work. A chest radiograph was relatively normal. Pulmonary function tests demonstrated marked impairment of ventilation and of the diffusing capacity. Bronchography demonstrated severe generalized dilatation of all bronchi in both lungs. This syndrome, severe bronchial damage after almost fatal exposure to SO_3, appears to be relatively more common than past medical literature would indicate.

The third patient was a 39-year-old man with a history of three successive episodes of pneumonia followed by an empyema of the left pleural space at the age of 2 years. Since that time he had developed cyanosis and hemoptysis during upper respiratory infections. The breath sounds were decreased at the base of the left lung and there were coarse rales, and an impaired percussion note in this area. Bronchography showed cylindrical and saccular bronchiectasis isolated to bronchi of the left lower lobe. The diseased lung was removed with complete relief of symptoms. Dr. D. V. Bates, Associate Professor of Medicine, McGill University, pointed out that in adults symptomatic localized disease should always be removed. Where both lower lobes are involved, and where the procedure is too radical, then antibiotics and postural drainage become the mainstays of therapy. Occasionally much lung may be safely removed, where heavily infected sputum cannot be controlled by more conservative measures. Pulmonary function tests are used as an aid in evaluating the functional capabilities of the tissue which will remain after surgery.

A 59-year-old man with a 10-year history of cough productive of a small amount of mucopurulent sputum each day, began to experience dyspnea, which increased progressively for the two years prior to consultation. He smoked 20 cigarettes per day. Scattered rhonchi were present. Breath sounds were transmitted well, and there was evidence of hyperinflation. Sputum culture yielded *H. influenzae*. Administration of tetracycline cleared up the sputum. A chest radiograph and bronchogram were normal. The maximum mid-expiratory flow rate was decreased to one-third normal, yet lung volumes were nearly normal. Dr. Christie made the diagnosis of chronic bronchitis. He pointed out that this is clearly an entity with its own etiology, pathology, and complications, and that it is a common cause of incapacity. Early in the disease there is only cough and expectoration. Later, dyspnea on exertion appears. This may be followed by either chronic infected asthma in which there is severe bronchospasm which is reversible and treatable, or by pulmonary emphysema in which irreversible tissue damage is present. The patient presented had the former type of disease. The first salient principle of therapy is to remove the patient from atmospheric pollution. He must be removed from areas of industrial pollution, from dusty occupations, and must stop cigarette smoking. Secondly, antispasmodics, of which ephedrine is still the best, afford some relief. The third problem, that of purulent sputum, is a distressing problem. Antibiotics will convert the sputum to one of a mucoid character. However, when the antibiotic (usually tetracycline at a dosage of 0.5 g. per day) is discontinued, the sputum becomes purulent again. Maintenance therapy with antibiotics leads to a high incidence of toxic effects, and so it is preferable to reserve the antibiotics for major complications, such as bronchopneumonia. Cortisone has often been used in therapy for these patients. The Medical Research Council conducted a trial which demonstrated that, during the first six weeks, cortisone has a beneficial effect, but thereafter no beneficial effect is evident, and indeed the toxic effects of cortisone give the drug-treated group of patients a worse prognosis. This drug should therefore not be used in these patients except as part of the therapy during a particularly severe acute bout of pneumonia. The patient must thereafter be weaned from the drug.

A man with chronic cough and a two-year history of dyspnea on exertion presented with acute dyspnea, fever, and chest pain at the site of the left nipple. A chest film showed patchy densities from apex to base bilaterally, suggesting an acute diffuse pneumonia. The patient became drowsy and then unconscious. Arterial puncture was performed and examination of the blood showed a pCO_2 of greater than 100 mm. Hg, and a pH of 7.1. The serum bicarbonate value was normal, demonstrating that this was acute respiratory acidosis, leading progressively to CO_2 narcosis. Therapy for such a patient consists firstly of recognizing and treating the CO_2 narcosis. Diagnosis is made only by arterial puncture. Therapy is carried out by performing a tracheotomy, and then utilizing a cuffed tube and positive-pressure respirator to ventilate the patient. As the therapy is pursued the pCO_2 will fall, and right heart failure will generally clear. The acute process leading to the CO_2 narcosis is treated immediately by large doses of antibiotics, usually with penicillin at a level of 5,000,000 units per day. Any patient with emphysema who enters the hospital with heart failure or a more severe febrile episode should immediately be given large doses of penicillin. CO_2 narcosis has now been recognized as a cause of death in fulminating pneumonia, septicemia, status asthmaticus, and anterior horn cell disease, and this should be considered during the evolution of these disease processes.

A 46-year-old woman, pregnant for the ninth time, was admitted in acute distress with cough, dyspnea, and weight loss of one month's duration. Two years prior to admission she had received x-ray therapy for an enlarged hilar lymph node. A chest film showed coarse reticulation throughout both lungs from apices to bases. The carbon monoxide diffusing capacity was slightly lowered on exercise. The first principle of therapy here was to secure a firm tissue diagnosis by lung biopsy. Thoracotomy was performed, and a tissue

diagnosis of sarcoidosis was made. The course of this disease is difficult to prognosticate. If the patient is deteriorating, cortisone (and antituberculous therapy as well) is given regardless of the x-ray appearance, since the correlation between x-ray changes and the changes in pulmonary function are often poor. This patient was given cortisone and improved.

A 55-year-old man with mild cyanosis, mild clubbing of the fingers, and Raynaud's phenomenon presented with cough and shortness of breath of one month's duration. Diffuse reticulation was evident radiologically throughout the lung fields. The carbon monoxide diffusing capacity was very low and increased little with exercise. There was an absence of peristaltic activity in the lower esophagus on fluoroscopy. Lung biopsy demonstrated diffuse fibrotic thickening of all alveolar walls. This was a case of pulmonary scleroderma with few cutaneous manifestations.

An apparently well man was referred because of a chest radiograph demonstrating many tiny calcific nodules less than 1 mm. in diameter scattered evenly throughout both lungs. This was a case of pulmonary alveolar microlithiasis, a disease of unknown origin, in which calculi of calcium carbonate and calcium phosphate form in the alveoli. His brother had a similar chest film.

C. A. GORESKY

"ALLERGY AND COLLAGEN DISEASES"

Chairman: *Dr. Jacques Léger*, Montreal
Panelists: *Dr. Bram Rose*, Montreal
Dr. R. H. More, Kingston
Dr. L. Morissette, Montreal
Dr. L. G. Johnson, Montreal

This session was presented by the Canadian Academy of Allergy

The speakers were introduced by the Chairman DR. JACQUES LEGER, Vice-President of the Canadian Academy of Allergy, who then proceeded to outline the broad spectrum of diseases encompassed by the term "collagen disorders".

Dr. Léger cited a number of examples of lesions produced in the experimental animal following the introduction of foreign protein that led to the concept that similar morphological lesions found in the human, in a variety of diseases, occurred on the basis of hypersensitivity. He pointed out that there was good evidence for the existence of an "auto-immune" reaction in diseases such as primary thyroiditis and nephritis, but that an antigen-antibody reaction was far from proven in all of the disorders which were to be discussed.

Dr. Bram Rose, Associate Professor of Medicine, McGill University, and Associate Physician, Royal Victoria Hospital, was asked to discuss some of the collagen diseases. Noting that these may all be manifestations of a deviation in the antibody-forming systems of the body, the so-called dysproteinemias, Dr. Rose first referred to disseminated lupus erythematosus in which condition there is evidence at the present time of the presence of six or seven antibody systems. He then referred to the associated conditions of scleroderma, dermatomyositis, polyarteritis and rheumatic fever, and pointed out that there was often great difficulty in separating these conditions one from the other. The features of two or more of these syndromes were not infrequently present at one time, and if one followed the course of the disease, progression from one to the other was frequently observed. He referred to the familiar experience of observing a typical case of rheumatoid arthritis developing into a classical picture of disseminated lupus erythematosus, and again of a clinical picture of dermatomyositis evolving into clinical scleroderma while the patient was being followed up. Recognition of this sequence of events has led to the coining of the term "overlap syndrome" to characterize those disorders presenting the features of two or more entities which in the past have been regarded as specific processes.

Dr. Rose also referred to the very high familial incidence of many of these conditions, which again suggested that there was a common deviation in the antibody-forming systems. In addition to the now commonly recognized clinical overlap, Dr. Rose pointed out that there was also an overlap of the abnormal proteins present in these conditions. For example, an overlap of rheumatoid factor, L. E. factor and anti-DNA may be found in rheumatoid arthritis, Sjögren's syndrome and disseminated lupus erythematosus.

Dr. R. H. More, Professor and Head, Department of Pathology, Queen's University, was called upon by the Chairman to discuss some of the pathological features of these conditions. Dr. More stated that these varied conditions possessed many pathological features in common, but this did not necessarily imply that the morphological changes were manifestations of the same disease. For example, the histological features of an abscess induced by a variety of etiological agents were indistinguishable. In the same manner, the presence of common histological features in the collagen diseases did not necessarily imply a common etiology.

The injection of an antigen into a non-sensitized animal induced a large mononuclear phagocyte response. The phagocytes then picked up the extracellular antigen and in about 10 days an increased cellular reaction was present, with plasma cells appearing at about two weeks. The end picture was that of an exudative response.

In such a sensitized animal the re-injection of antigen two weeks later resulted in an explosive reaction characterized by edema, fibrinoid, separation of the collagen and the presence of a few polymorphonuclear cells. In observing the progress of the reaction one subsequently noted the disappearance of exudate and the appearance of mononuclear cells, and the maturing out of plasma cells. There were thus three types of granulomatous response to the introduction of this specific antigen.

Dr. More drew attention to the similarity of the pathological lesions found in rheumatic fever, sulfonamide sensitivity, the pericarditis of disseminated lupus erythematosus and rheumatoid arthritis, and illustrated this similarity with lesions taken from the pericardium, the auricular wall, and the synovium, all showing a similar mononuclear reaction. The sequence of events in these lesions reveals much that is similar. He also pointed out that the arteritides existing in polyarteritis, acute rheumatic fever and disseminated lupus erythematosus were indistinguishable histologically. Exposure following systemic sensitization resulted in lesions characteristic of an active "Arthus" reaction, but were not pathognomonic of an immune reaction.

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Less specific lesions were also present in these conditions.

The pathological evidence again suggests that there may be an overlap in reaction to antigen. Stressing the fact that the pathological findings were not necessarily manifestations of the same disease, Dr. More raised the questions of why the lesions were of a different order and why different reactions occurred in different individuals.

Dr. L. Morissette, Associate Professor of Medicine, University of Montreal, in discussing certain aspects of immunohematology expressed some surprise in finding himself participating in a panel on allergy. He pointed out that 30 years ago the only connection between the hematologist and the allergist was the presence of the eosinophil in some cases of allergy. He felt that the desirability of a hematologist in this field was brought about by Hargreaves' discovery of the L.E. cell in bone marrow puncture.

Dr. Morissette drew attention to the hematological manifestations of lupus erythematosus, in which condition, hemolytic anemia, leukopenia, thrombocytopenia, purpura and hemorrhages all may develop if the patient lives long enough. These manifestations may culminate in pancytopenia. He suggested that autoimmune mechanisms which were very similar to other autoimmune hematological phenomena appear to be present.

Dr. L. Johnson, Assistant Professor of Medicine, McGill University, reviewed some of the manifestations of rheumatoid arthritis and stressed that this condition was a systemic disease with joint manifestations rather than primarily a disease of joints. In support of this he drew attention to the frequent presence of lesions in the eyes, lungs, heart and other tissues. Serum protein changes as well as anemia were also accompaniments. He added that there were also numerous antigen-antibody systems present in rheumatoid arthritis.

Dr. Johnson also emphasized the clinical overlap between rheumatoid arthritis and other collagen diseases by citing instances of rheumatoid arthritis evolving into lupus erythematosus, rheumatic fever with valvular heart disease diagnosed in childhood and presenting as full-blown lupus erythematosus in early adult life, and the presence of features in patients with rheumatoid arthritis that are usually clinically associated with polyarteritis nodosa. Arteritis and peripheral neuritis were more commonly seen in patients with rheumatoid arthritis treated by steroids but also occurred in untreated patients. Although clinical overlap is frequently observed, Dr. Johnson agreed with Dr. More that great caution was necessary in interpreting similar pathological lesions as being of the same etiology.

A number of interesting questions were raised by the audience, and were directed to various members of the panel by the Chairman.

In answer to a question on the incidence of amyloidosis in collagen diseases other than rheumatoid arthritis, Dr. More replied that he had never found it in other collagen diseases.

The panel was asked to discuss the occurrence of rheumatoid arthritis in some cases of agammaglobulinemia. Dr. Rose explained that in such cases there was not a complete absence of gamma globulins and the condition should rather be referred to as hypogammaglobulinemia. Furthermore, some antibody systems arose in connection with other fractions of the globulin and were found, for example to involve the β-globulins. The occurrence of rheumatoid arthritis in "aggamaglobulinemia" was therefore not inconsistent with the concept of a deviation in the antibody-forming systems. Dr. Rose added that he felt that the term "connective tissue disease" was not a good one and that "disease of the reticuloendothelial system or antibody systems" was more suitable.

Dr. Morissette was asked to comment on the hydralazine syndrome. Dr. Morissette remarked that this was another area where hematology and allergy came together. The L.E. phenomenon indicated the presence of antibody. The nature of the antigen was unknown but was probably nuclear material. He cited the example of agranulocytosis occurring after the administration of aminopyrine, where aminopyrine acted as a haptene, which in combination with protein formed an antigen leading to the formation of an antibody against the granulocytes. Similarly hydralazine appeared to act as a hapten, which, in combination with globulin, gave rise to a factor which was responsible for the presence of the L.E. cell phenomenon in the hydralazine syndrome.

Dr. Rose then discussed another method of demonstrating the L.E. cell phenomenon. Tissue plus circulating antibody gives rise to a lesion which can be demonstrated by adding serum containing anti-DNA and fluorescein from patients with diffuse lupus erythematosus, to smears of buccal mucosa. A positive test causes fluorescence of the cell nuclei.

Dr. Léger asked Dr. More whether autoantibody formation could be considered a normal physiological process which assumed importance only if excessively stimulated. Dr. More conceded that autoimmune antibodies might be formed normally but were not detectable. Dr. More also stressed the fact that it was not necessary to postulate autoimmune mechanisms, since an antigen from any source could conceivably give rise to the conditions under discussion.

Dr. Léger asked Dr. Rose to comment on the treatment and prognosis of the collagen diseases. Dr. Rose listed the prodromal, clinical, and laboratory features of D.L.E. (disseminated lupus erythematosus) and considered the cytoid body or cotton wool exudate sometimes observed in the fundus to be pathognomonic of this condition. The electrophoretic pattern is nonspecific and of no value in the diagnosis. With respect to treatment, Dr. Rose felt that if the disease were present in a mild form, without involvement of the heart and kidney, no treatment was indicated, but that it was important to avoid the use of sulfonamide drugs and hydralazine. Mild symptoms could readily be controlled by salicylates, and if a patient was not doing well it was often helpful to add one of the antimalarial drugs to the salicylate therapy. He pointed out that remissions and exacerbations were characteristic of the disease.

If the disease progressed to involvement of the heart and kidney, use of a 30-mg. equivalent of prednisone for a long period of time should be contemplated. He observed that 4-8 mg. of methylprednisolone would often suffice for a maintenance dosage. If convulsions occurred during exacerbations, then it was most important to increase the steroid dosage, and to treat other manifestations symptomatically as they arose. He had noted instances of allergy to diphenylhydantoin

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(Dilantin) used in the treatment of the convulsions occurring in D.L.E.

In discussing the treatment of rheumatoid arthritis, Dr. Johnson agreed with the use of the antimalarial drugs, noting that they were relatively innocuous preparations and the response was sometimes dramatic. He disagreed with the figure of 70% improvement sometimes quoted after the use of antimalarial drugs in rheumatoid arthritis and felt that 15% was probably a more realistic figure. He noted that the sclerosing lesions in scleroderma did not respond to steroids, and that the antimalarial drugs, chelating agents and relaxin were of doubtful value in this condition. Dr. Johnson stressed the importance of a basic regimen in rheumatoid arthritis and the maintenance of joint mobility with an adequate program of physiotherapy.

Dr. Léger then asked Dr. Morissette to comment on the role of splenectomy in the treatment of autoimmune diseases. Dr. Morissette stated that the spleen probably acts in a variety of ways in the autoimmune diseases. Possible functions were sequestration and phagocytosis of the damaged cells and a hormonal role in cytopoiesis in bone marrow. The presence of the spleen was also necessary for some immune reactions to take place, since allergic reactions were less marked in splenectomized animals and humans. There was, however, no evidence that splenectomy was of value in the treatment of these conditions.

Dr. Rose pointed out that a large variety of circulating and intracellular antibody systems existed. After injury to tissue, for example to the pancreas, there appeared in 24 hours a precipitating antibody to the damaged tissue. The question arises, what causes a deviation of reaction to normal tissue?

Dr. Johnson was asked to comment upon the role of the steroids in the treatment of necrotizing arteritis. He replied that necrotizing arteritis may be seen in untreated rheumatoid arthritis, but was much more common after the use of steroids. He commented upon the paradox of treating polyarteritis with steroids. He felt that when necrotizing arteritis appeared in rheumatoid arthritis treated by steroids the patient should be slowly and carefully weaned off this treatment. The overlapping of this group of diseases was again illustrated by reference to two cases of arteritis with peripheral neuritis occurring in rheumatoid arthritis.

Dr. Morissette was asked to comment on the incidence of the "butterfly rash" in D.L.E. He replied that the rash in this condition may be discoid and remain as such for many years. It was not generally appreciated that in D.L.E. the skin lesions may be flitting and appear very late.

Discussion was closed by Dr. H. L. Bacal of Montreal who thanked the panel on behalf of the Canadian Academy of Allergy.

K. R. MACKENZIE

(To be continued)

GOLF TOURNAMENT AT THE 94th ANNUAL MEETING

Further details are now available concerning the Golf Tournament, held at the Royal Montreal Golf Club, Isle Bizard, on Thursday, June 22. The draw comprised 71 golfers, principally from Montreal, but also from many distant centres including Vancouver, Edmonton, Toronto and Winnipeg. Golfing conditions were excellent and the complete draw, played in threesomes and foursomes, finished by 6 p.m.

At the post-tournament dinner, skillfully chaired by Dr. J. McKay of Montreal, those present were asked to consider the feasibility of establishing a Canadian Medical Golfers Association to stimulate more active participation in the annual tournament and to provide its members with certain additional privileges.

Prizes and trophies were presented to the following participants:

Dr. M. M. Sereda—low gross—score 78, won on 19th hole; Ontario Cup.
Dr. Y. Dion—2nd low gross—78.
Dr. T. Hale—3rd low gross—78.
Dr. St. Germain—score 79.
Dr. G. Young—score 79.
Dr. W. Roy—1st low net—66; Quebec Trophy.
Dr. P. W. Des Ruisseaux—2nd low net—68.
Dr. Henderson—3rd low net—69.
Dr. P. Cronin—4th low net—71.
Dr. Y. Prévost—5th low net—71.
Dr. A. Dérôme—most honest golfer.

LADIES' GOLF TOURNAMENT

The ladies' golf tournament was held on Thursday, June 22, at Mount Bruno, Que. It was a beautiful day and the event was considered to be both pleasant and successful.

Twenty-six ladies appeared at the course, about one-third being "out of towners" and the rest from Montreal and district.

The T. Eaton Trophy for low gross was tied for by two 7-handicap players—Mrs. Malcolm D. Thorp of Sarnia, Ont., and Mrs. George Maughan of Montreal. The winner was Mrs. Thorp after a sudden-death 19th hole playoff. Drug firms very generously donated prizes for the various events. The winners were as follows:

Mrs. Malcolm D. Thorp, Sarnia—1st low gross; Eaton Trophy.
Mrs. George Maughan, Montreal—2nd low gross.
Mrs. D. D. Munro, Montreal—1st low net.
Mrs. R. Cronin, Montreal—2nd low net.
Mrs. Herbert Monks, Montreal—3rd low net.

MRS. C. MILLER BALLEM,
MRS. GAETAN JARRY,
Co-chairmen

CLASSIFIED ADVERTISEMENTS

Please send copy to the Advertising Department, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

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The publishers of the Canadian Medical Association Journal are constantly on the alert for misrepresentations in classified advertisements. However, it is not always possible to detect inaccuracies. The publishers therefore urge all respondents to investigate thoroughly the opportunities offered in these pages before any commitments are made.

Classified advertisements must be at the office of the Journal not later than three weeks prior to date of issue.

Positions Wanted

RADIOLOGIST, experienced, available after September 1, 1961. Certified in diagnostic and therapeutic radiology. Reply with full particulars to Box 558, CMA Journal, 150 St. George Street, Toronto 5, Ont.

CANADIAN G.P. with anesthetic and psychiatric experience wishes to join clinic in west. Consider rural practice if conditions right. Some capital. Currently in west and available for interview until September 1. Reply to Box 569, CMA Journal, 150 St. George Street, Toronto 5, Ont.

CANADIAN GRADUATE, age 31, married, completing training in specialty of general surgery at a western Canadian university; desires employment in Winnipeg, Man., with a surgeon or group or single doctor. For further particulars please write Box 570, CMA Journal, 150 St. George Street, Toronto 5, Ont.

Positions Vacant

OPHTHALMOLOGIST WANTED for general English-speaking hospital. Applicant should be licensed and certified, or eligible to be certified, in the Province of Quebec. Reply to Box 946, CMA Journal, 150 St. George Street, Toronto 5, Ont.

OTOLARYNGOLOGIST to take charge of E.N.T. Department with a large well-established Toronto group, good salary and opportunity for partnership. Reply to Box 229, CMA Journal, 150 St. George Street, Toronto 5, Ont.

ASSISTANT WITH DEFINITE OPPORTUNITY FOR PARTNERSHIP, wanted by busy general practitioner, in surburban Toronto area, on or before January 1, 1962. Salary commensurate with experience, plus bonus arrangement and car allowance. Please write stating age, experience, marital status and religion to Box 360, CMA Journal, 150 St. George Street, Toronto 5, Ont.

OPHTHALMOLOGIST—$15,000 per annum guaranteed, plus commission to take full charge of department, excellent hospital facilities, immediately available to successful applicant. Large city close to Toronto. This is a most attractive opening to a competent physician. State full particulars in first letter. Reply to Box 196, CMA Journal, 150 St. George Street, Toronto 5, Ontario.

WANTED.—GENERAL PRACTITIONER or internist willing to do general practice in well-equipped suburban Toronto clinic, composed of general practitioners and specialists. Good salary, regular schedule, opportunity for partnership after one year. Please reply with full particulars to Box 216, CMA Journal, 150 St. George Street, Toronto 5, Ont.

GENERAL PRACTITIONERS for large fully-equipped Toronto clinic offering immediate busy practice with regular schedule and opportunity for partnership. Reply to Box 484, CMA Journal, 150 St. George Street, Toronto 5, Ontario.

ASSISTANT WANTED FOR BUSY GENERAL PRACTICE in association with three other doctors, in town of 7000, near Toronto. Open hospital 5 miles away. Early opportunity for more permanent arrangement if mutually suitable. Available July 1. Full details please to Box 520, CMA Journal, 150 St. George Street, Toronto 5, Ontario.

CERTIFIED OR BOARD ELIGIBLE UROLOGIST with California license for Los Angeles area group. Apply to M. Fosburg, 1403 650 S. Grand, Los Angeles, California, U.S.A.

WANTED.—Psychiatrist to head a mental health centre in Sydney, Nova Scotia. Salary: $11,500 with four annual increments of $500 each. Opportunity for private practice. Other information promptly supplied upon request. Apply Lewis N. McMillan, Chairman, Mental Health Board, Provincial Bldg., Prince St., Sydney, N.S.

WANTED.—ASSISTANT with view to partnership required for large Alberta country practice with excellent 35-bed hospital. Preferably married. Knowledge anesthesia and obstetrics preferable. Salary $650 monthly with car expenses. Applicants to supply photo, references, past training and state religion to Box 548, CMA Journal, 150 St. George Street, Toronto 5, Ont.

WANTED IMMEDIATELY—ASSISTANT for general practice, southern Ontario. Salary $700 to $800 plus car expenses, depending on experience. Partnership to right man, January 1, 1962. No investment required. Partly furnished house to rent, $75 per month, heat and electricity supplied. Reply to Box 549, CMA Journal, 150 St. George Street, Toronto 5, Ontario.

ALBERTA GENERAL PRACTICE.—Edmonton clinic group desires assistant in field of general practice. Excellent facilities include full laboratory and x-ray services. Applicants should have at least two years' approved internship and should include full details of training, etc. Reply to Box 552, CMA Journal, 150 St. George Street, Toronto 5, Ontario.

DIAGNOSTIC RADIOLOGIST—certified or eligible for certification, wanted in western Canadian city. Hospital with well-equipped x-ray department and some private practice. Reply with full particulars to Box 555, CMA Journal, 150 St. George Street, Toronto 5, Ont.

PHYSICIAN WITH ONTARIO LICENCE REQUIRED for chronic and convalescent hospital, 340 beds, with complete rehabilitation and physical medicine department, x-ray and laboratory. Full-time, forty-hour-week, pension, life insurance and sick benefits. Apply to Director of Medical Services, Riverview Hospital, Windsor, Ontario.

WANTED.—GROUP IN WESTERN CANADA requires an internist, Canadian certification, or equivalent. Guaranteed salary based on qualifications, with year end bonus. Applicants are reminded that a lively, friendly personality is essential to success in this area. Reply stating age, qualifications and other particulars to Box 560, CMA Journal, 150 St. George Street, Toronto 5, Ont.

STAFF PSYCHIATRIST-PHYSICIANS, IMMEDIATE OPENINGS. Canadian graduates eligible. 1800-bed mental hospital, salary commensurate with training and experience, housing and food allowance in addition; progressive wage scale, liberal personnel policies. State retirement and social security. Write: Superintendent, Montana State Hospital, Warm Springs, Montana, U.S.A.

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MEDICAL NEWS *in brief*

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SYMPOSIUM ON EMERGENCY RESUSCITATION

An international symposium on emergency resuscitation, including discussions of rescue breathing and closed chest cardiac massage, is being arranged by the Norwegian Association of Anesthetists. The symposium will be held in Stavanger, Norway, from August 21 to August 25, 1961.

The scope of the symposium will include manually operated appliances, but not devices which need an external source of power. Recent developments in methods of teaching will receive attention. The language of the symposium will be English.

The organizers of the symposium consider that a discussion by an international group of experts on the problems associated with emergency resuscitation, and with the best means of teaching the improved methods to as wide a section of the community as possible, will be of considerable importance to organizations concerned with rescue work (military medical corps, Red Cross, rescue squads, etc.) and to medical advisers to such organizations.

Those interested in attending are requested to write as soon as possible to the President of the Norwegian Association of Anesthetists, Dr. Ivor Lund, Ulleval sykehus, Oslo, Norway.

HISTOPLASMOSIS AND THE CITY DWELLER

The latest facet in the emerging pattern of urban histoplasmosis is provided by a recent study of an epidemic among Boy Scouts in the town of Mexico, Missouri, reported by Furcolow *et al.* (*New England J. Med.*, 264: 1226, 1961). The investigation was set in motion by an outbreak of illness characterized by chills, high fever and cough in four boys, all of whom had the clinical features and x-ray findings appropriate to histoplasmosis. Positive skin and serologic tests later confirmed the diagnosis. All four had onset of illness within 12 to 14 days after having worked, with a group of 64 scouts from four local troops, raking leaves and debris in a large city park. In the summer and fall of 1955, this park was inhabited by thousands of starlings and their droppings almost completely covered the ground. At the time of the epidemic, there was still evidence of considerable bird droppings, especially in the southeastern quarters of the park. This study and other evidence suggest that city dwellers contract histoplasmosis by contact with point-sources of growth of the organism and not by the casual inhalation of windborne spores disseminated throughout the city. A pattern of urban histoplasmosis that includes at least four distinct sources of infection has emerged: visits to farms or prior rural residence; exposure to imported farm soils or manures; exposure in urban structures frequented by birds; and exposure in open urban areas. In each of these forms of exposure, urban infection can be related directly to exposure to sources contaminated with bird excreta. This urban epidemic of histoplasmosis in Mexico, Missouri, illustrates the fourth source of infection. Frequent isolations from this soil containing excreta indicate a high degree of contamination with *Histoplasma capsulatum*. It is postulated that starlings, and perhaps other gregarious birds that frequent cities, may be important in creating sites of florid fungus growth within communities in areas of both high and low prevalence of histoplasmosis.